



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 60

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 60

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

Volume 60 consists of four chapters and a set of indices.

In the first chapter, the chemistry of five-membered ring fluorinated heterocycles is covered by K. Burger, U. Wucherpfennig, and E. Brunner of the Technical University of Munich, Germany. Polyfluoroheteroaromatic compounds were last reviewed in Volume 28 of this series in 1981. The chemistry of polyfluoroheterocycles with six-membered rings was covered by M. J. Silvester in Volume 59; the necessity of treating the subject in two different chapters is an indication of the increased importance that polyfluoroheterocycles have attained over the past decade.

Thiopyrylium, selenopyrylium, and telluropirylium salts are reviewed by G. Doddi (Rome, Italy) and G. Ercolani (Catania, Italy). Whereas the chemistry of the analogous pyrylium salts was the subject of a special supplementary volume in our series in 1982, no exhaustive previous review of the other chalcogenopyrylium salts has been available.

E. Alcalde of Barcelona, Spain, presents a review of the class of heterocyclic betaines in which the positive charge is located on a pyridinium ring and the negative charge on an azolium ring. A unified picture of what has been a somewhat neglected class of highly dipolar heterocycles is presented.

Finally, C. J. Easton, C. M. M. Hughes, G. P. Savage, and G. W. Simpson (Adelaide and Melbourne, Australia) review the cycloaddition reactions of nitrile oxides with alkenes. Although previous reviews of this subject have appeared, the synthetic potential of this reaction has recently been the object of intensive study.

Volume 60 is an "index volume" and includes three indices. The author index and the title index cover the entire series since its inception, and list in alphabetical order the titles and authors of all the chapters that have

appeared. However, the subject index covers only Volumes 55 through 60. Volume 40 contained the cumulative subject index for Volumes 1–40; Volumes 41–45 were covered in Volume 45, and Volumes 46–53 in Volume 53. Volume 54, as a monograph volume, contained its own subject index.

Alan R. Katritzky

Fluoro Heterocycles with Five-Membered Rings

KLAUS BURGER, UWE WUCHERPFENNIG, AND
ENNO BRUNNER

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I. Overview

Fluorine and/or perfluoroalkyl groups positioned strategically in target molecules may considerably modify chemical properties, biological activity, and selectivity [76MI3; 79MI4; 81AG(E)647; 82MI1, 82MI2; 87MI4, 87T3123; 91MI2]. A number of fluoro- and perfluoroalkyl-substituted pharmaceuticals, agrochemicals, dyes, and polymers have already been commercialized. The number of patents concerning fluorinated compounds shows a tendency to grow. Thus, one can anticipate that fluoro-containing compounds will continue to play a significant role in medicinal and agricultural chemistry as well as in material science (90JOC4448).

The exchange of hydrogen by fluorine does not alter steric bulk much because of the similarity of the Van der Waals radii (H: 1.20 Å, F: 1.35 Å) and may be regarded an isosteric substitution. The postulated quasi-

isosterism between CH_3 and CF_3 groups (72MI1; 82T871; 87T3123) is still a controversial issue [92JFC(57)229]. The Van der Waals radii of a trifluoromethyl group and of a methyl group are 2.7 \AA / 2 \AA , whereas the Van der Waals volumes are 42.6 \AA^3 / 16.8 \AA^3 [90AG(E)1320]. The steric demand of a trifluoromethyl group seems to be close to that of an isopropyl group.

It has been suggested that there should be little or no effect on bond length when a methyl group attached to a carbon atom is replaced by a trifluoromethyl group [83JFC(23)147]. Therefore, this transformation should result in minimal disruption to an enzyme–substrate complex [90AG(E)1320].

Important differences in chemical reactivity of fluorinated compounds are based on the difference in carbon—fluorine (456–486 kJ/mol) and carbon—hydrogen bond energy (356–435 kJ/mol); on the difference in electronegativity between fluorine and hydrogen (Pauling scale: 4 / 2.1), which can gradually alter and even invert reaction behavior of adjacent centers; and on the ability to participate in hydrogen bonding as an electron pair donor (87JA8067).

With increasing fluorination the C—C bond length shortens and consequently the bond strength increases. This phenomenon is unique among halogens (75MI1). For example, the C—C bond in 1,1,1-trifluoroethane or hexafluoroethane is 59 or 42 kJ/mol more stable than that of ethane, respectively (73MI1; 75MI2). Therefore, introduction of trifluoromethyl groups stabilizes molecules. Other properties of the trifluoromethyl group include electronegativity similar to that of oxygen (65JPC3284) and high lipophilicity [lipophilicity scale (83MI2; 86JPS987): $\text{F} < \text{CF}_3 < \text{OCF}_3 < \text{SCF}_3$] enhancing the absorption rates of drugs, improving their transport rates *in vivo*, and helping to permeate certain body barriers.

Fluorine introduced into biologically active molecules can block metabolism. The high carbon—fluorine bond energy renders fluorine resistant to many metabolic transformations (91MI3). In this context 5-fluorouracil is a typical example: It inhibits the enzyme thymidylate synthase, which catalyzes methylation of deoxyuridylate to provide deoxythymidylate (72MI2), an essential component for DNA synthesis. 5-Fluorouracil can still be transformed into 5-fluorouridylate (and hence is incorporated into RNA) and is accepted as enzyme substrate. The difference in C—H / C—F bond energy, however, renders C-methylation at the 5-position impossible. This makes 5-fluorouracil and its analogues efficient cytotoxic agents.

Since an increasing number of enzymes have been characterized in terms of their three-dimensional structure, and since the mechanisms by which reactions occur at their active sites have been elucidated, it should

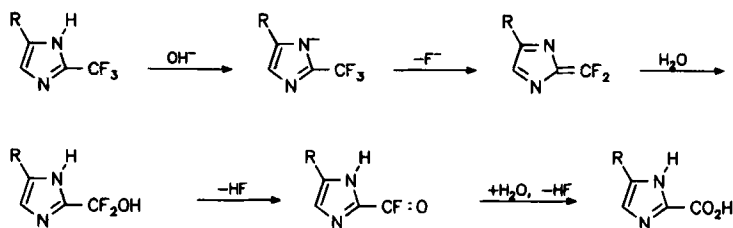
be possible to make a rational design of mechanism-based fluorinated drugs.

A. REACTIVITY OF FLUORINE AND TRIFLUOROMETHYL GROUPS

The high carbon-fluorine bond energy renders the fluorine substituent a bad leaving group in S_N2 reactions and resistant to many metabolic transformations. By contrast, in addition–elimination processes fluorine shows superior leaving group ability relative to hydrogen and the other halogens. These properties have led to the development of very effective mechanism-based enzyme inhibitors (68MI1; 73MI2; 76MI4; 83MI1; 85MI1; 88MI1; 90MI3).

Although the trifluoromethyl group is often considered to be chemically inert (53JA4091, 53JCS922), it is known to undergo a variety of reactions. The hydrolytic behavior of a trifluoromethyl group is very much dependent on its position in a molecule. Trifluoromethyl groups of aromatic compounds undergo hydrolysis, but only in acidic media (47MI1). Trifluoromethyl groups attached to carbon atoms possessing acidic hydrogen atoms are susceptible to hydrolysis in basic media (88S614). For this reason 3,3,3-trifluoroalanine is unstable in basic medium at room temperature. The trifluoromethyl group undergoes hydrolysis to give a carboxylate (66CB1944). Trifluoromethyl groups attached to certain positions of heterocyclic systems undergo facile base-induced hydrolysis, e.g., the trifluoromethyl group in 2-trifluoromethylimidazole (79JOC2902; 80JOC3831) (Scheme 1).

Via a similar reaction sequence, consisting of a series of successive elimination/addition steps, 5-amino-4-trifluoromethyloxazoles can be transformed into 5-amino-4-methyloxazoles on treatment with LiAlH_4 (90S357). The ability to eliminate fluoride ions from trifluoromethyl and perfluoroalkyl groups on treatment with bases allows *in situ* generation of valuable synthetic fluoro-containing building blocks (88S614; 90JOC4777).



B. STRATEGIES FOR THE INTRODUCTION OF FLUORINE AND PERFLUOROALKYL GROUPS INTO ORGANIC MOLECULES

There are two fundamentally different strategies by which fluorine and/or perfluoroalkyl (or polyfluoroalkyl) groups can be introduced into target molecules: (a) Direct introduction—by direct substitution of hydrogen by fluorine and perfluoroalkyl groups in a late step of the reaction sequence or by functional group transformations in a late step of the reaction sequence; and (b) introduction of fluorine and perfluoroalkyl groups by application of fluorine-containing building blocks, derived from readily available starting materials.

Although the first approach is more straightforward, provided that suitable fluorinating and perfluoroalkylating reagents are available, control of regio- and stereoselectivity is often difficult to achieve. Because of the high reactivity of most fluorinating agents, many functional groups already present in the molecule also may be transformed in an undesired way. Therefore, they have to be appropriately protected. Protection and deprotection of these groups require additional reaction steps. Furthermore, many of the reagents currently used for direct introduction of fluorine and perfluoroalkyl groups are expensive, toxic, corrosive, and sometimes explosive.

Consequently, the building block strategy (78T3; 81MI1) for introduction of fluorine and perfluoroalkyl groups into organic molecules represents an attractive alternative concept. The method is often synthetically more elegant and allows one to introduce fluorine and perfluoroalkyl groups in a regio- and stereoselective manner into a target molecule.

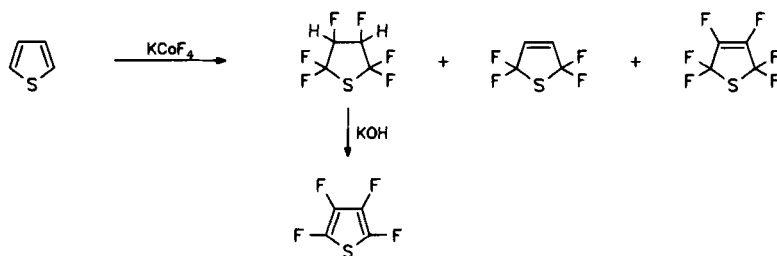
Since partially fluorinated heterocyclic compounds are important in both academia and industry the synthetic state of the art has been reviewed regularly (74MI1; 76MI2; 77MI1; 81AHC1; 91MI1).

II. Direct Introduction

A. INTRODUCTION OF FLUORINE INTO FIVE-MEMBERED HETEROCYCLES

1. Radical H/F Substitution

Introduction of fluorine into heterocyclic systems can be achieved using molecular fluorine. However, direct fluorination is known to be notoriously regio- and stereo-unselective. Extensive work is still going on to overcome these problems (79MI3; 86CRV997; 89MI1). In special cases



SCHEME 2

selective fluorination can be achieved under certain reaction conditions [86BAU1901; 89JFC(45)99].

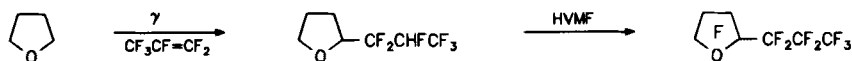
2. Fluorination/Dehydrofluorination

Fluorination/dehydrofluorination is the classical route to perfluoroaromatics. However, yields are low, when this method is applied to nitrogen-containing aromatic systems. In contrast, fluorinated furans [69JCS(C)2585; 70JCS(C)2146] and thiophenes [69CC27; 71JCS(C)346, 71JCS(C)352] can be synthesized in good yields on reaction with high-valency metal fluorides (HVMF) (60M11) and subsequent dehydrofluorination (Scheme 2).

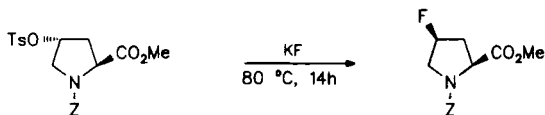
This route is especially valuable for the transformation of electron-rich heteroaromatic compounds into their fluorinated analogues, which are not suitable for the nucleophilic exchange route. The method has been extended by addition of fluorinated olefins. The fluoroolefins add in a radical process to the 2-position of tetrahydrofuran, followed by perfluorination to give the perfluorinated 2-alkyl-substituted tetrahydrofurans in excellent yields [84JFC(25)523; 85JFC(29)323] (Scheme 3).

3. Electrochemical Fluorination

This fluorination technique is difficult to employ for selective fluorination and gives high yields only for poly- and perfluorinated compounds [67M11; 79CJC2617; 87CL1435; 88JFC(39)435; 89T1423; 90JFC(48)257; 91T549].



SCHEME 3



SCHEME 4

4. Nucleophilic Displacement Reactions

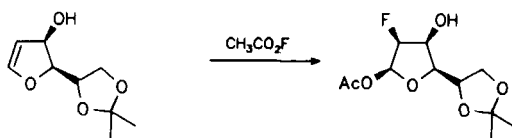
Introduction of fluorine into organic molecules via nucleophilic displacement reactions remains problematic since the fluoride ion often behaves as a base rather than as a nucleophile (73MI2, 80CRV429). Halogen exchange reactions are of major importance in the synthesis of fluorinated heteroaromatic compounds, where the activating influence of the nitrogen ring atom strongly affects the rate of the nucleophilic displacement process.

Crown ethers have been used to enhance nucleophilic activity of metal fluorides (85JHC1621; 86T2677). Halogen exchange reactions are also possible with hydrogen fluoride (79GEP2729762) and antimony fluoride (90JA9671). *cis*- and *trans*-4-fluoro-L-proline derivatives have been synthesized from the corresponding *trans*- and *cis*-*O*-tosylated 4-hydroxy-L-prolines on treatment with potassium fluoride [65B(4)2507]. Many other functional groups are susceptible to replacement by fluoride ions [81AG(E)647; 92CRV505] (Scheme 4).

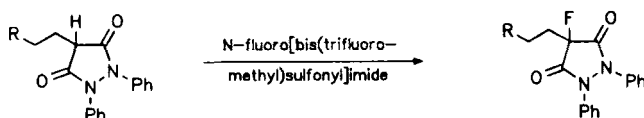
5. Electrophilic Fluorination Reactions

Although fluorine mostly reacts as a radical species, under certain conditions it can also act as an electrophile. Some cases of a direct fluorination of electron-rich C—H bonds have been described (80NJC239; 84TL449; 87JOC2769; 88JOC2803).

The first electrophilic fluorinating agents containing O—F bonds were gaseous, hygroscopic, toxic, and often explosive. Examples include trifluoromethyl hypofluorite (CF_3OF ; 78MI1), which was applied to convert cytosine into 5-fluorocytosine (76JA7381); trifluoroacetyl hypofluorite (CF_3COOF), which was used to fluorinate pentafuranoses (87MI5); and cesium fluorooxy sulfate (CsSO_4F ; 84MI8) (Scheme 5).



SCHEME 5



SCHEME 6

In recent years a second generation of reagents for electrophilic fluorination has been developed. These reagents contain N—F bonds. They are more stable, easier to handle, and often more selective. These reagents could be useful in the synthesis of bioactive molecules where selectivity and mild reaction conditions are essential.

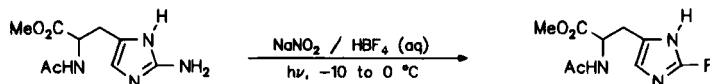
This new class of reagents includes *N*-fluoroperfluoropiperidine; dihydro-*N*-fluoro-2-pyridone; *N*-fluoro-*N*-alkyl sulfonamides; *N*-fluoropyridinium salts (90JA8563); *N*-fluoroquinuclidinium salts [86JFC-(32)461]; *N*-fluoroperfluoroalkyl sulfonamides; 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts (Selectfluor; 92CRV505); and *N*-fluoro-bis(trifluoromethyl)sulfonylimide [92JFC(58)361], which was used to transform some pharmacologically active compounds into their fluorinated analogues. *N*-Fluorosultams have been used to achieve enantioselective fluorination (88TL6087). Their synthetic potential for selective fluorination of heterocyclic compounds has not been exploited (Scheme 6).

6. Balz–Schiemann Reaction

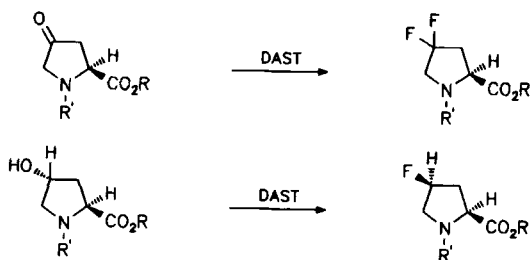
Regioselectively fluorinated heteroaromatic compounds can be obtained on transformation of amino groups using the classical Balz–Schiemann reaction (65M11; 71JA3060) or modified routes. When a solution of suitably protected 2-amino- and 4-amino-DL-histidines in 50% fluoroboric acid are treated with sodium nitrite and subsequently photolyzed, the 2-fluoro- and 4-fluoro-DL-histidine derivatives are obtained (73JA4619, 73JA8389) (Scheme 7).

7. Transformation of Hydroxy and Carbonyl Groups into CF and CF₂ Moieties

Diethylaminosulfur trifluoride (DAST) has become one of the most important fluorinating agents (75JOC574, 75JOU72; 76JOU973; 87OR513). It is mainly used to transform alcohols, aldehydes, or ketones into mono- or difluorinated compounds. It has been used successfully in sugar, nucleo-



SCHEME 7



SCHEME 8

side (85TL3, 85TL5; 88CPB1554, 88JCS(P1)549; 89CC955), and amino acid chemistry [93JFC(60)179, 93JFC(60)193]. Fluorination of alcohols occurs with inversion of configuration (Scheme 8).

α -fluorination of heterocyclic sulfoxides with DAST has been accomplished in the presence of antimony trichloride (88TL5729).

8. Displacement Reactions of Metallated Fragments

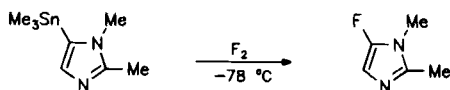
The reaction of metallated heterocyclic species with elemental fluorine enables regioselective fluorination at low temperatures (86BSF930). This strategy seems promising. However, the synthetic potential has not been fully exploited (Scheme 9).

B. INTRODUCTION OF POLYFLUOROALKYL AND PERFLUOROALKYL GROUPS INTO FIVE-MEMBERED HETEROCYCLES

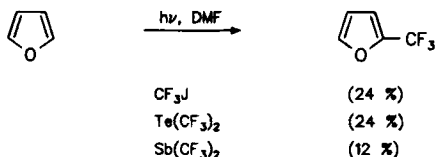
The trifluoromethyl group is the most prominent fluorinated side chain. An excellent review on all aspects of the introduction of the trifluoromethyl group into organic compounds is available (92T6555). The trifluoromethyl group can be introduced as radical, nucleophilic and electrophilic species as well as by functional group transformations.

1. Introduction of Trifluoromethyl Groups as Radical Species

The trifluoromethyl radical is electrophilic in nature (61JA4732) and may be generated from precursors photochemically, thermally, by chemical reactions, and electrochemically (92T6555). A large number of precursors



SCHEME 9



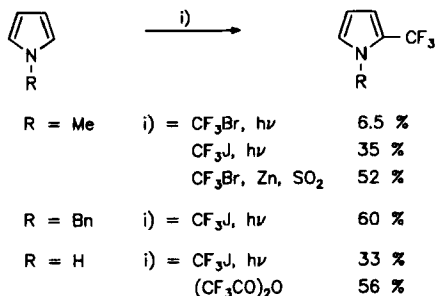
SCHEME 10

are available for photochemical generation of trifluoromethyl radicals: iodotrifluoromethane (78CPB1247; 82JOC2867; 83JOC3220; 84JOC1060; 91BCJ2255), bromotrifluoromethane (88BCJ3531), *N*-trifluoromethyl-*N*-nitrososulfonamides (82TL3929; 86BCJ447), diazotrifluoromethane, bis-(trifluoromethyl)mercury, tris(trifluoromethyl)antimony, and bis(trifluoromethyl)tellurium [90JFC(46)265] (Scheme 10).

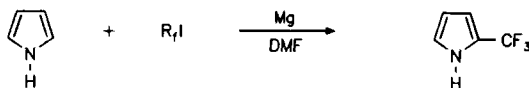
Bis(trifluoromethyl)tellurium and trifluoromethyl iodide have been shown to be suitable trifluoromethylation reagents for furan [90JFC(46)265].

Trifluoromethyl radicals have been generated thermally from bis-(trifluoromethyl)tellurium [90JFC(46)265], iodotrifluoromethane [81JFC(17)345], bromotrifluoromethane, hexafluoroacetone, or *N*-trifluoromethyl-*N*-nitrosotrifluoromethylsulfonamide.

Trifluoromethyl radicals were generated electrochemically from solutions of partially neutralized trifluoroacetic acid (79CJC2617; 91T549) or bromotrifluoromethane (89T1423) and chemically from the reaction of trifluoromethyl bromide with zinc / sulfur dioxide, sodium dithionite [90JCS(P1)2293], or xenon difluoride with trifluoroacetic acid (88JOC4582); from bis(trifluoromethyl)peroxide [86BCJ215; 88BCJ3549; 89JCS(P1)909; 90JFC(46)423; 92JFC(58)173]; and from sodium trifluoromethane sulfinat (91TL7525). Some of the radical trifluoromethylations of five-membered heterocycles studied so far show a remarkable degree of regioselectivity (Scheme 11).



SCHEME 11



SCHEME 12

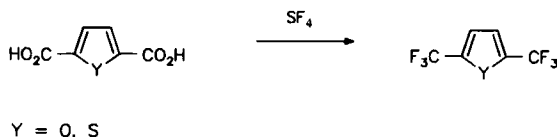
Imidazole and *N*-acyl histidine esters undergo facile photochemical perfluoroalkylation on treatment with perfluoroalkyl iodides at room temperature [82JOC2867; 84JOC1060]. The imidazole ring of the tripeptide Pyr-His-Pro-NH₂ was preferentially trifluoromethylated in a photochemical reaction with trifluoromethyl iodide, yielding both isomers, namely the 2- and the 4-trifluoromethylated compounds, in a total yield of 20% (90TL5705). Perfluoroalkyl radicals formed on treatment of perfluoroalkyl iodides with magnesium in dimethylformamide can be trapped by pyrrole, providing 2-perfluoroalkylpyrroles [88JFC(39)289] (Scheme 12).

2. Transformation of Trichloromethyl Groups into Trifluoromethyl Groups

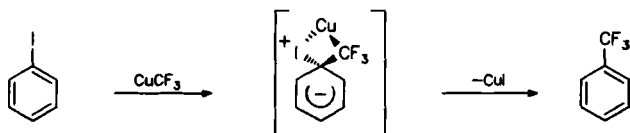
Trichloromethyl groups can be readily transformed into trifluoromethyl groups on treatment with antimony trifluoride (61MI1), with HF either on its own or in the presence of antimony trifluoride, aluminum trichloride / fluorotrichloromethane, or silver tetrafluoroborate.

3. Transformation of Carboxylic Groups into Trifluoromethyl Groups

Sulfur tetrafluoride [74OR1; 75JOU456; 81JFC(17)179; 85OR319; 87JFC(37)429; 90JA9671; 91JHC225] as well as DAST in the presence of sodium fluoride (87OR513) are capable of converting carboxylic groups into trifluoromethyl groups. Many other functional groups already present in the molecule have to be appropriately protected, otherwise they undergo undesired transformations. Trifluoromethyl-substituted thiophenes have been prepared via this route [90JFC(46)445] (Scheme 13).



SCHEME 13



SCHEME 14

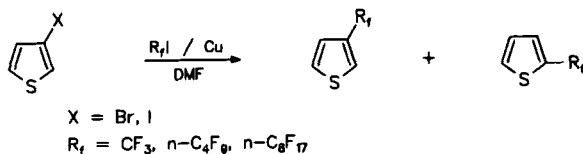
4. Introduction of Trifluoromethyl Groups via Trifluoromethyl Copper

Trifluoroalkyl iodides react with aromatic and heteroaromatic halides in the presence of copper to give perfluoroalkyl-substituted compounds [68USP3408411; 69T5921; 77CPB3009; 80JCS(P1)661, 80JCS(P1)2755; 90JFC(46)137]. The reactive species in this reaction was shown to be CuCF_3 (86JA832; 89CC1633; 92T189) (Scheme 14).

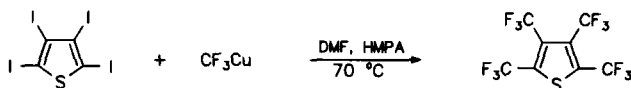
The nucleophilic nature of this reagent is confirmed by the ρ -value +0.46 obtained from the crude Hammett plot of the reaction of *p*-substituted iodoaromatics with the trifluoromethylating system sodium trifluoroacetate / copper iodide [88JCS(P1)921]. Consequently, electron-withdrawing substituents enhance reactivity, whereas electron-donating substituents ($-\text{OH}$, $-\text{NH}_2$) inhibit the reaction.

From the coupling reaction of halothiophenes with perfluoroalkyl iodides and copper a mixture of 3- and 2-perfluoroalkylated thiophenes is obtained; the 3-substituted product being the major isomer [85JFC(27)291] (Scheme 15).

Likewise, 2-perfluoroalkyl-substituted pyrroles were obtained on reaction of perfluoroalkyl iodides and pyrroles in the presence of stoichiometric amounts of copper (87MI3). Polytrifluoromethylation can be achieved by the same methodology with polyiodinated aryl and heteroaryl compounds (92T189) (Scheme 16).



SCHEME 15



SCHEME 16

5. Electrophilic Trifluoromethylation

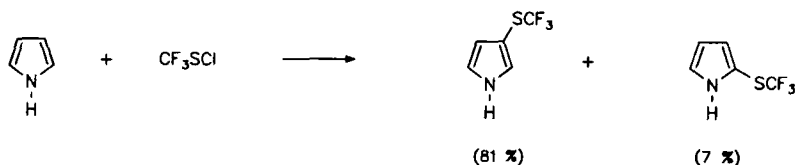
(Trifluoromethyl)diarylsulfonium salts (84JOU103) as well as (trifluoromethyl)dibenzothiophenium salts and their seleno analogues are convenient, easy to handle reagents for the electrophilic transfer of trifluoromethyl groups. They can trifluoromethylate electron-rich systems (90TL3579). They represent reagents with an immense preparative potential for trifluoromethylation of electron-rich heteroaromatic systems, which has not been developed. Trifluoromethyl cations have been generated in the gas phase on ^{60}Co γ -irradiation of tetrafluoromethane. They react with pyrrole, furan, and thiophene regiospecifically to give trifluoromethylated compounds (91JA4544).

C. INTRODUCTION OF TRIFLUOROMETHOXY AND TRIFLUOROMETHYLTHIO GROUPS

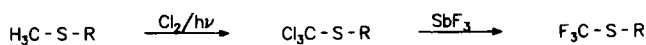
The trifluoromethoxy and the trifluoromethylthio group are highly lipophilic substituents (91CC993). Therefore, their introduction into biologically active compounds is of current interest.

Incorporation of the trifluoromethyl thiol moiety into heterocyclic systems may be achieved by several methods (92T6633). Trifluoromethylthio-lation of heteroaromatic compounds with trifluoromethansulfonyl chloride occurs via a free radical chain mechanism (77CB67) (Scheme 17).

Trifluoromethylthio-substituted heteroaromatic systems are available by a multistep procedure, namely photochlorination of the corresponding methyl thioether and subsequent halogen exchange on treatment with antimony trifluoride (52ZOB2216; 54ZOB887) (Scheme 18).



SCHEME 17



SCHEME 18

III. Introduction of Fluorine and Perfluoroalkyl Groups into Five-Membered Heterocycles via Cyclocondensation Reactions

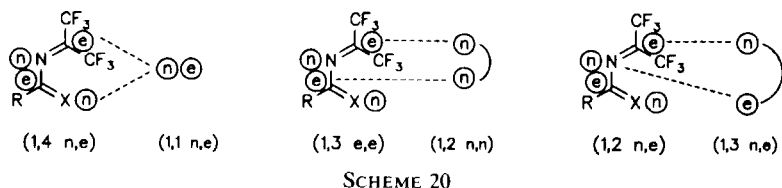
Cyclocondensation reactions starting from two components are possible only when both have two reactive centers. By far the most common version is an initial electrophilic/nucleophilic interaction yielding a linear product, followed by a second electrophilic/nucleophilic interaction in the final cyclization step (85MI2). The ring-forming condensation step is controlled by a series of rules (Baldwin rules: 76CC734). There are various types of such interactions (Scheme 19).

The distance between the two reactive centers in each component is given by numbering the skeleton atoms; e.g., 1,3 nn represents a 1,3-dinucleophilic compound. (For further details of this classification see 85MI2.) Based on this concept, for instance, bis(trifluoromethyl)-substituted hetero-1,3-dienes (F_3C)₂C=N—C(R)=X (X = O, S, NR') formally should be able to undergo three types of condensation reactions to give five-membered ring systems, classified by the number of the skeleton atoms of the hetero-1,3-diene being incorporated into the newly formed ring system (Scheme 20).

Furthermore, heterocyclic ring systems can also be constructed by intramolecular radical, carbene, and nitrene reactions. Condensation reactions provide routes to heterocyclic systems with a well-defined substitution pattern. Since many fluoro-containing building blocks (91MI5) with suitable additional functional groups for cyclocondensation reactions are readily available, fluorine or/and polyfluorinated substituents can be introduced into five-membered heterocycles regioselectively, via one or both starting compounds. Cyclocondensation reactions can be divided into several subgroups, according to the charge pattern of the starting materials and the number of skeleton atoms incorporated into the newly formed ring system.



SCHEME 19

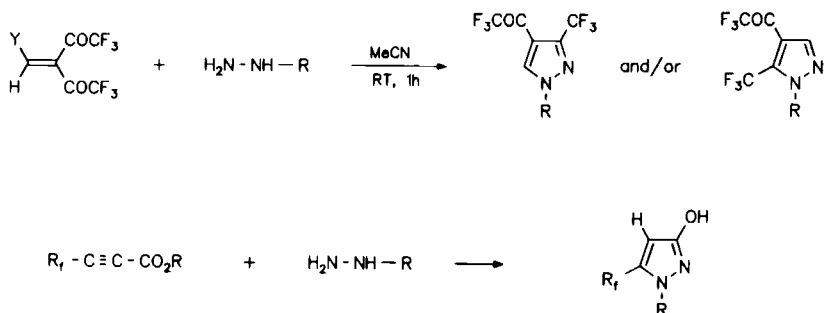


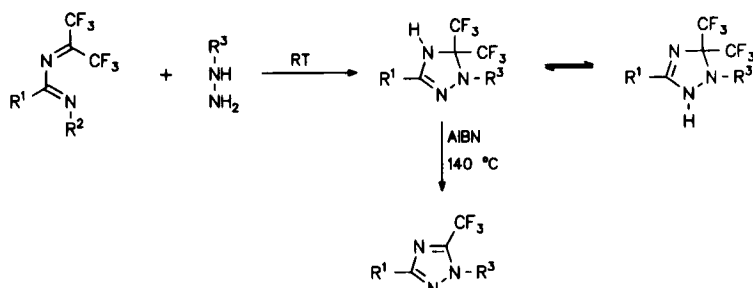
A. [3 + 2] CYCLOCONDENSATION REACTIONS

1. Condensation Reactions of Fluoro-containing 1,3-Dielectrophilic with 1,2-Dinucleophilic Building Blocks

A large number of fluoro-containing [1,3-electrophilic/electrophilic (ee)] building blocks are known. Partially fluorinated pentan-2,4-diones [86S340; 87JHC739; 91JFC(51)283]; α -fluoro- β -ketoesters (81BCJ3221; 91S1013); methyl 2-cyano-2-fluoroacetate (89UKZ420); 2-trifluoroacetylvinylether, -vinylthioether, -vinylamines (87JHC739; 92H791); 4,4-bis(trifluoromethyl)-1,3-diazabuta-1,3-dienes (88CZ109); 3-perfluoroalkyl propiolates [90JFC(48)123]; 3-perfluoroalkylpropio- and acrylonitriles [81JOU219; 87JFC(37)371]; alkynyl trifluoromethyl ketones; 1,1-bis(perfluoroalkyl)-substituted olefins (90BAU2338); 2-fluoro-2-perfluoroalkyl enol phosphates (88CL819), etc., react with (1,2 nn) building blocks, like hydrazines and hydroxylamines, to give pyrazoles and isoxazoles, respectively (Scheme 21).

The cycloadducts obtained often undergo elimination reactions with heteroaromatization under the reaction conditions or on heating as demonstrated by the transformation of bis(trifluoromethyl)-substituted 1,2,4-triazolines into 5-trifluoromethyl-1,2,4-triazoles in the presence of azobisisobutyronitrile (AIBN) (88CZ109) (Scheme 22).



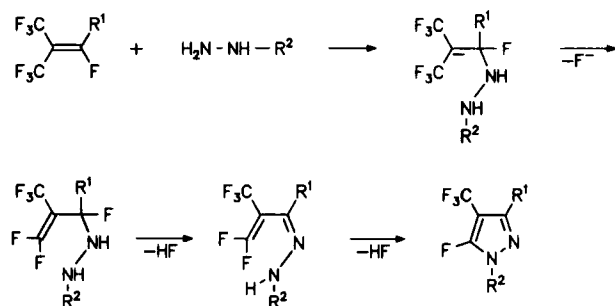


SCHEME 22

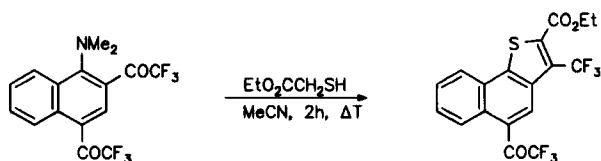
The reaction of 1,1-bis(trifluoromethyl)-2-fluoro olefins with (1,2 nn) compounds is of preparative and mechanistic interest, because a priori this type of olefin does not represent a 1,3-dielectrophilic species. The second electrophilic center is generated during the reaction (Scheme 23).

The anion formed on nucleophilic attack of the hydrazine stabilizes by fluoride and subsequent HF elimination to give an α,β -unsaturated hydrazone, which undergoes an electrocyclic ring closure with HF elimination to yield 5-fluoro-4-trifluoromethylpyrazoles. The single fluorine bonded to C(5) can be exchanged by a wide variety of nucleophiles (88S194; 90BAU2338).

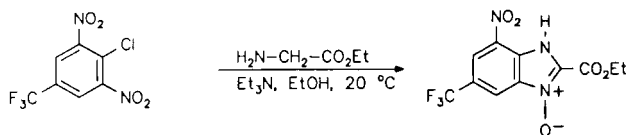
Aromatic compounds susceptible to nucleophilic substitution reactions having substituents with an electrophilic center adjacent to the position of nucleophilic attack, e.g., *N,N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine, also are (1,3 ee) building blocks. They react with



SCHEME 23



SCHEME 24



SCHEME 25

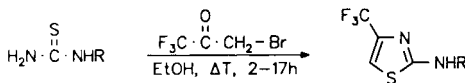
(1,2 nn) species, like ethyl thioglycolate, benzylmercaptan (92H103), amino acid esters (89S550), hydrazines, and hydroxyl amines (90S481), to yield trifluoromethyl-substituted naphthothiophenes, benzindoles, benzindazoles, and naphthoisoxazoles, respectively (Scheme 24).

2,6-Difluorobenzonitrile and methylthioglycolate cyclize to give 4-fluorobenzo[*b*]thiophene [91JFC(54)104]. The reaction of trifluoromethyl-substituted 2,4-dinitrochloro- and 2,6-dinitrochlorobenzene with alkyl thioglycolates and amino acid esters at room temperature in the presence of triethylamine follows the same mechanistic concept to yield trifluoromethyl-substituted benzothiazole and benzimidazole derivatives [88JFC(38)327] (Scheme 25).

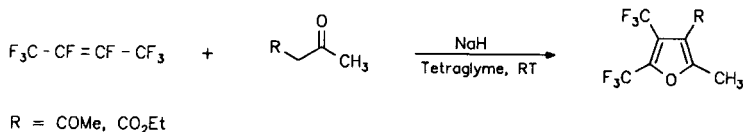
2. Condensation Reactions of 1,3-Dinucleophiles with Fluoro-containing 1,2-Dielectrophilic Building Blocks

Widely used 1,3-dinucleophiles are thioamides, thioureas, and amidines. With 1-bromo-3,3,3-trifluoro-2-propanones [55JOC499, 55USP2726237; 88IJC(B)1051; 91JHC907, 91JHC1017, 91MI4], ethyl 2-bromo-4,4,4-trifluoro-3-oxobutanoate (91JHC907), and ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate (85JHC1621; 91JHC1003) they are transformed to give trifluoromethyl-substituted thiazoles and imidazoles (Scheme 26).

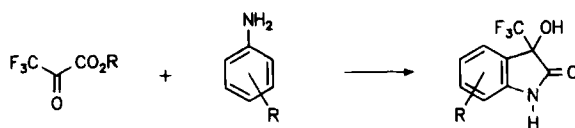
Acetylacetone and alkyl acetoacetates, both (1,3 nn) species, and perfluorobut-2-ene, a masked (1,2 ee) compound, react in the presence of sodium hydride at room temperature to give 2,3-bis(trifluoromethyl)furans [83JCS(P1)1239] (Scheme 27).



SCHEME 26



SCHEME 27



SCHEME 28

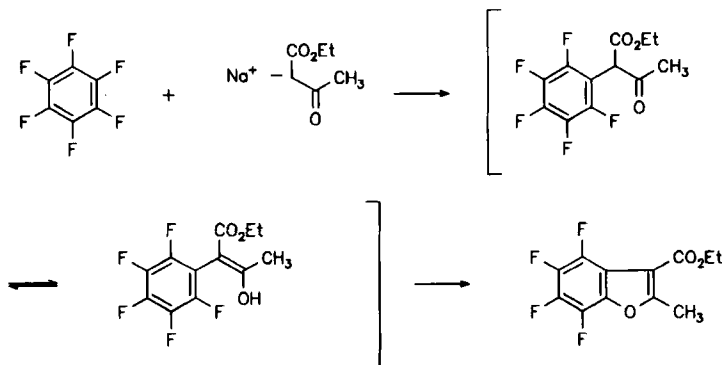
Similarly, trifluoropyruvates and related α -iminoesters represent 1,2-dielectrophilic building blocks. With anilines and phenols they undergo C-alkylation in an *o*-position followed by ring closure to form γ -lactams and γ -lactones (86BAU1895; 87BAU2332, 87BAU2646; 89BAU1512) (Scheme 28).

Fluoro-substituted annulated five-membered heterocycles are available via stepwise nucleophilic displacement reactions of perfluorinated or polyfluorinated aromatic compounds by 1,3-dinucleophiles. On reaction of hexafluorobenzene with the sodium salt of ethyl acetoacetate the 3-ethoxycarbonyl-2-methylcumarone is formed [64DOK(158)926; 69KGS778] (Scheme 29).

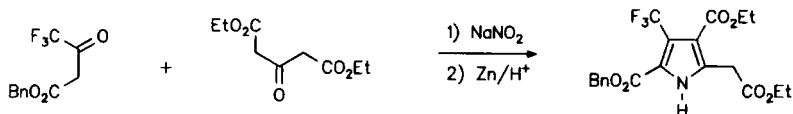
Based on the same mechanistic concept, syntheses of perfluorobenzo[*b*]thiophenes and partially fluorinated indoles are described [67JCS(C)865, 67JCS(C)869, 67JCS(C)1189; 68JCS(C)1225, 68TL4049].

3. Condensation Reactions of Fluoro-containing 1,3-Nucleophilic/Electrophilic with 1,2-Nucleophilic/Electrophilic Building Blocks

2-Amino-4,4,4-trifluoroacetylacetates represent three atomic building blocks having a nucleophilic and an electrophilic center in a 1,3-position. They readily react with (1,2 ne) compounds like CC, CO, CN double



SCHEME 29



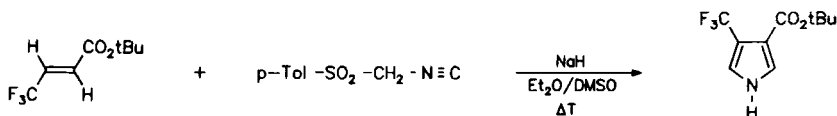
SCHEME 30

bonds and CC, CN triple bonds to provide five-membered heterocyclic ring systems. On reaction with diethyl acetone-1,3-dicarboxylate, 3-trifluoromethylpyrroles are formed (83BRP2107304) (Scheme 30).

Perfluorothiophenol and acetylene react at 600°C to yield tetrafluorobenzo[*b*]thiophene (89JOU201). Similarly, 2,3,4,5,6-pentafluoro-1-thionaphtholate and dimethyl acetylene dicarboxylate give fluorinated naphtho[*b*]thiophenes [89JFC(43)393].

4. Condensation Reactions of 1,3-Nucleophilic/Electrophilic with Fluoro-containing 1,2-Nucleophilic/Electrophilic Building Blocks

Since many fluoro-containing (1,2 ne) building blocks with CC, CO, and CN double bonds are readily available, this type of cyclocondensation reaction is extremely flexible and includes the elegant tosylmethyl isocyanide (TOSMIC) strategy for synthesis of five-membered heterocycles [74AG(E)789; 76TL285; 77AG(E)339, 77JA3532; 80MI1].

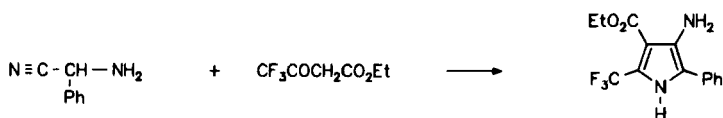


SCHEME 31

Tosylmethyl isocyanide can react i.a. with fluoro- and perfluoroalkyl-substituted olefins, e.g., tert-butyl (E)-4,4,4-trifluoro-2-butenate [91JFC(53)61] and β -perfluoroalkyl-substituted α,β -unsaturated ketones (88CL1891) to provide 3-trifluoromethylpyrroles. The latter are also accessible from isocyanoacetates and 3-nitro-2-hydroxy-1,1,1-trifluoroalkanes, which *in situ* are transformed into olefins on treatment with acetic anhydride/DBU (89BCJ3386) (Scheme 31).



SCHEME 32



SCHEME 33

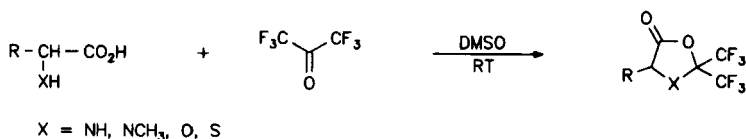
Trifluoroacetonitrile (62JOC2085, 62JOC3248), trifluoroacetimidoyl chlorides (90TL2717), and trifluoroacetimidoyl fluorides (66JOC789) react with sodium azide or alkyl azides to give 5-trifluoromethyltetrazoles (Scheme 32).

Trifluoromethyl-substituted aminopyrrole derivatives of pharmaceutical significance have been synthesized from α -aminonitriles and ethyl 4,4,4-trifluoroacetoacetate (73USP4198502; 74USP4212806) (Scheme 33).

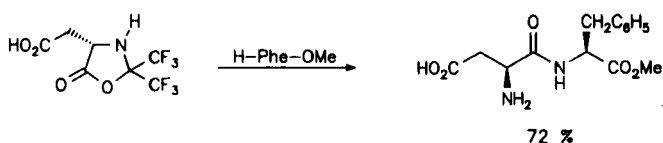
Hexafluoroacetone was shown to be an extremely versatile (1,2 ne) building block for the introduction of a geminal pair of trifluoromethyl groups as well as a single trifluoromethyl group into five-membered heterocyclic systems (87MI2).

Cyanoformamidines having both nucleophilic and electrophilic capacity in a 1,3-position react with hexafluoroacetone to give five-membered heterocycles (86CB2127). Hexafluoroacetone, certain perfluorinated or partially fluorinated ketones, aldehydes, and imines react with α -functionalized carboxylic acids, α -amino, α -*N*-alkylamino, α -*N*-arylamino (60JA2288; 66CB1461), α -hydroxy (66CB2880), and α -mercapto acids [87JFC(35)87] to give five-membered heterocyclic systems (Scheme 34).

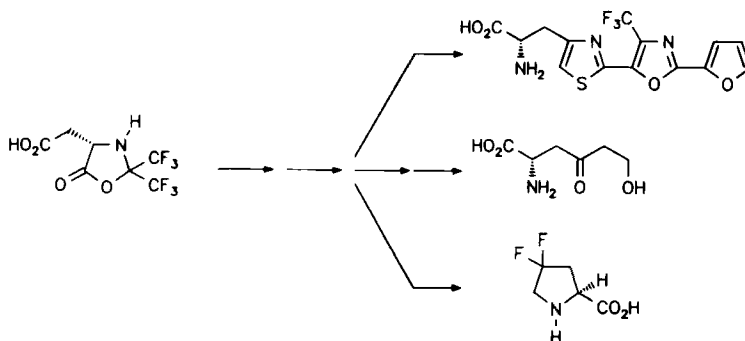
The hexafluoroacetone derivatives are highly volatile compounds. They can therefore be used for gas chromatographic analysis of mixtures of α -amino and α -hydroxy acids. As activated esters they can be employed for the synthesis of small peptides, azapeptides, and depsipeptides. Applying this strategy to ω -carboxy- α -amino acids, a preparatively simple



SCHEME 34



SCHEME 35

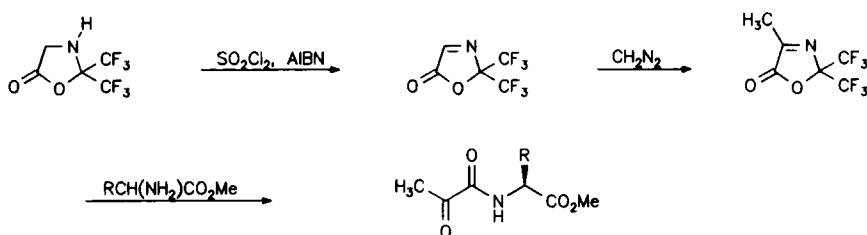


SCHEME 36

regioselective carboxyl group activation is possible (91CZ77). The efficiency of this method was demonstrated by a two-step synthesis of aspartame (90CZ249). Protection of the α -amino group and activation of the α -carboxylic group is accomplished in only one step. Deprotection of the α -amino group occurs during aminolysis (Scheme 35).

Furthermore, these five-membered heterocycles show promising potential for the synthesis of various natural and nonnatural α -amino, α -hydroxy, and α -mercapto acids. Multifunctional α -amino acids can be selectively protected at the α -position, whereas other functionalities remain unprotected and can be derivatized further. Applying this strategy to aspartic acid, new preparatively simple stereoconservative routes lead to heterocyclic amino acids (92S1145), antibiotics like 5-hydroxy-4-oxonorvalin (HON, 92S1150), 5-substituted 4-ketoprolines [93AG(E)285; 93TL5879] and 4-fluoro- and 4,4-difluoro-prolines. Deblocking of the amino and the carboxyl group is achieved in one step on treatment with water/isopropanol at room temperature (Scheme 36).

2,2-Bis(trifluoromethyl)-4-methyl-2H-5-oxazolone, readily available from 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one, represents an activated pyruvate (79LA1547) (Scheme 37).



SCHEME 37

5. *Condensation Reactions of Fluoro-containing 1,3-Dielectrophilic with Fluoro-containing 1,2-Dinucleophilic Building Blocks*

Well-defined substitution patterns in the target molecules can be constructed by a combination of fluorine-free or fluoro-substituted (1,3 ee) components with fluorine-free and fluoro-substituted (1,2 nn) compounds. A representative example for the introduction of fluorine and fluoro-substituted groups into five-membered heterocycles via both educts is the reaction of fluoro-substituted chalcones and pentafluorophenyl hydrazine (88JIC773).

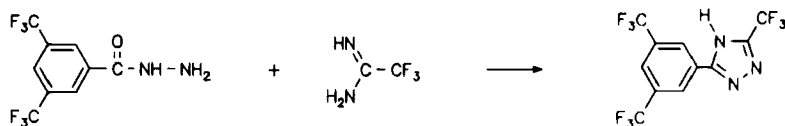
6. *Condensation Reactions of Fluoro-containing 1,3-Nucleophilic/Electrophilic with Fluoro-containing 1,2-Nucleophilic/Electrophilic Building Blocks*

Polyfluorinated target molecules are obtained when both building blocks are fluorinated and/or perfluoroalkylated. A typical example for this type of condensation is the synthesis of a tris(trifluoromethyl)-substituted 1,3,4-triazole from 3,5-bis(trifluoromethyl)benzhydrazide and trifluoroacetamidine (78BRP1510647).

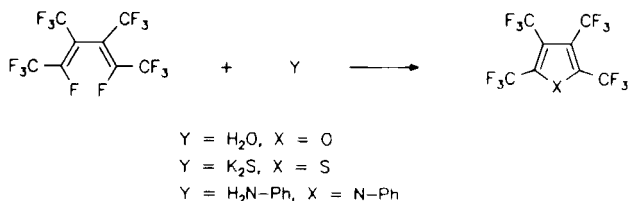
B. [4 + 1] CYCLOCONDENSATION REACTIONS

1. *Cyclocondensation Reactions of Fluoro-containing 1,4-Dielectrophilic with 1,1-Dinucleophilic Building Blocks*

1,4-Dielectrophilic species are 1,4-diketones, certain 1,3-dienes, α,β -unsaturated isocyanates, isothiocyanates, cyanates, and thiocyanates bearing electron-withdrawing (e.g., polyfluorinated and perfluorinated) substituents; the most frequently used 1,1-dinucleophiles are water, potassium sulfide, primary amines, and ammonia. From this repertoire of building blocks many combinations are possible. Tetrakis(trifluoromethyl)furans, thiophenes, and pyrroles have been synthesized from perfluoro-3,4-dimethylhexa-2,4-diene on addition of water, potassium sulfide, or aniline (90CC1127) (Scheme 39).



SCHEME 38



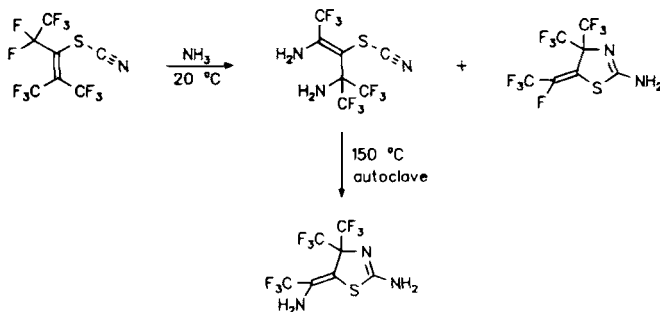
SCHEME 39

Perfluoro-2-methyl-3-thiocyanato-2-pentene reacts with ammonia to give a mixture of 2,4-diaminoperfluoro-4-methyl-3-thiocyanato-2-pentene and 2-aminoperfluoro-4,4-dimethyl-4,5-dihydro-5-ethylidene thiazole. The open-chain product is ring closed on heating up to 150°C in an autoclave (92BAU260, 92MI1) (Scheme 40).

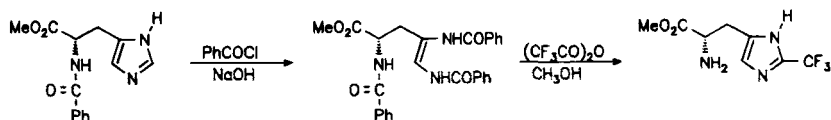
Another example for this mechanistic type is the reaction of 2-chloroperfluoro-1-thiocyanato-1-cyclohexene with gaseous ammonia at room temperature. The 2-amino-4,4,5,5,6,6,7,7-octafluoro-4,5,6,7-tetrahydro-benzothiazole initially formed, subsequently suffers a nucleophilic attack by ammonia and HF elimination to give 2-amino-4,4,5,5,6,6-hexafluoro-7-imino-4,5,6,7-tetrahydro-benzothiazole (91BAU2075).

2. Cyclocondensation Reactions of 1,4-Dinucleophilic with Fluoro-containing 1,1-Dielectrophilic Building Blocks

The 1,4-dinucleophilic building blocks used most are 1,2-disubstituted ethanes of the type $HXCH_2CH_2YH$, semicarbazides, thiosemicarbazides, hydroxamic acid amides, amidrazones, and 1,2-disubstituted aromatic and heteroaromatic compounds. 1,1-Dielectrophilic building blocks preferentially used are perfluorinated carboxylic acids and their derivatives, such as acid halides, anhydrides, imidoesters, nitriles, perfluoroalkyl chlorosul-



SCHEME 40



SCHEME 41

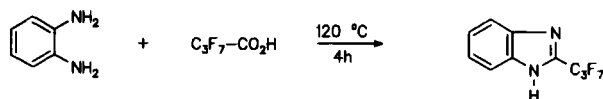
fonates and trichloromethyl perfluoroalkyl ketones. The perfluoroalkyl substituent enhances the electrophilic nature of these species. On combination of these building blocks many five-membered heterocycles with well-defined ring atom and substituent patterns can be synthesized.

Trifluoroacetic acid or trifluoroacetic acid anhydride reacts with hydroxamic acid amides, thiosemicarbazide, and 1,2-diaminopyridine to yield herbicidal active 1,2,4-oxadiazoles [78GEP(O)2801509], fungicidal-active 1,3,4-thiadiazoles (80USP4264616), and 2-trifluoromethyltriazolo[1,5-*a*]pyridines [80JFC(15)179]. 2-Trifluoromethyl-L-histidine was obtained from L-histidine on treatment with benzoyl chloride/sodium hydroxide and subsequent ring closure with trifluoroacetic anhydride (78JOC3403) (Scheme 41).

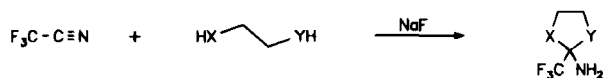
Similarly, with perfluoroalkanoic acids or the corresponding anhydrides, perfluoroalkyl groups can be attached to five-membered heterocyclic systems [81JFC(18)243] (Scheme 42).

Fluoroalkyl-substituted benzoxazoles and benzothiazoles can be synthesized from fluoroalkyliminoesters, which are readily available from fluoroalkylnitriles and alcohols or *o*-hydroxy- or *o*-mercaptoanilines [76JFC(8)295]. Glycols and thioglycols readily react with trifluoroacetonitrile at room temperature to give 2-amino-2-trifluoromethyl-1,3-dioxolanes, -1,3-oxothiolanes, and -1,3-dithiolanes (79IC2319) (Scheme 43).

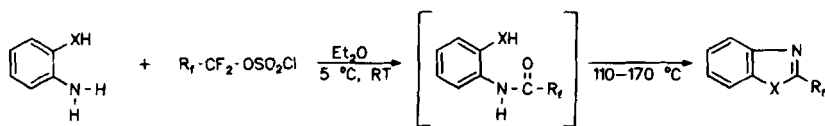
Like perfluorocarboxylic acid fluorides, perfluoroalkyl chlorosulfonates react with 2-aminophenols, 2-aminothiophenols, and 1,2-diaminobenzene to give *N*-acylated products. On subsequent heating ring closure occurs with formation of 2-perfluoroalkyl-substituted benzoxazoles, benzothiazoles, and benzimidazoles [90JFC(49)197] (Scheme 44).



SCHEME 42



SCHEME 43



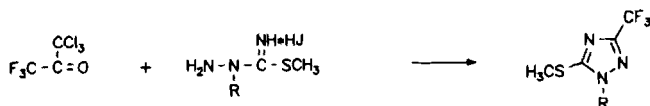
SCHEME 44

The only example where a ketone is successfully introduced as a (1,1 ee) building block is 1,1,1-trichloro-3,3,3-trifluoroacetone, which on heating with methylthioamidrazones is transformed into 3-trifluoromethyl-1,2,4-triazoles (83JHC1533). A plausible mechanistic interpretation for the elimination of a trichloromethyl group during the reaction seems to be a haloform cleavage of the adduct initially formed to give a *N*-trifluoroacetyl compound, which on heating undergoes ring closure (Scheme 45).

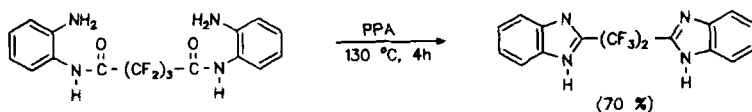
C. 1,5-CYCLOCONDENSATION REACTIONS

In certain cases the open-chain products of [3 + 2] and [4 + 1] condensation reactions can be isolated, and the ring closure can be done in a second step. Therefore, this reaction type is very suitable for testing the “Baldwin rules” (76CC734). *o*-Phenylenediamine can be monoperfluoroacylated on treatment with perfluoroacylfluorides at room temperature. On subsequent heating the *N*-acylated compounds undergo a 5-*exo-trig* ring closure and 2-perfluoroalkylbenzimidazoles are obtained. Via this strategy two benzimidazole moieties can be joint linearly, i.e. by perfluorinated alkyl chains [81JFC(18)243]. In an analogous process 2-perfluoroalkylbenzothiazoles are formed from 2-aminothiophenols [78JFC(12)271] (Scheme 46).

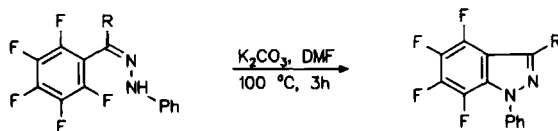
Phenylhydrazones of perfluorobenzaldehyde and 2,3,4,5,6-pentafluoroacetophenone cyclize on heating in the presence of potassium carbonate to give 4,5,6,7-tetrafluoroindazoles [90JFC(49)359]. A plausible mecha-



SCHEME 45



SCHEME 46



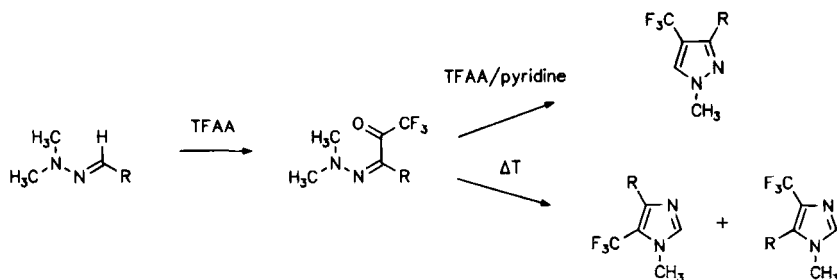
SCHEME 47

nism seems to be 1,5-electrocyclization of a heteropentadienyl anion initially formed and subsequent fluoride elimination with aromatization (Scheme 47).

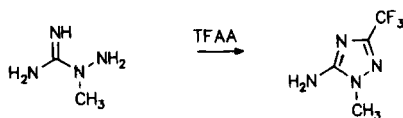
A large number of 1-, 2-, and 3-substituted 4,5,6,7-tetrafluoroindoles have been obtained via a similar route [68DOK(178)864; 69JGU1583; 70KGS381, 70KGS385, 70KGS622, 70MI1]. After *C*-trifluoroacetylation with trifluoroacetic anhydride, *N,N*-dialkylhydrazones from aliphatic and aromatic aldehydes can be transformed into trifluoromethyl-substituted pyrazoles and imidazoles (88JOC129, 88JOC519, 88TL5281; 90JHC487) (Scheme 48).

N-Methyl-*N*-trifluoroacetylaminoguanidine prepared from *N*-methyl-*N*-aminoguanidine and trifluoroacetic anhydride undergoes a 1,5-cyclocondensation reaction to give a pharmaceutically active trifluoromethylated 1,2,4-triazole (80FRP2477150) (Scheme 49).

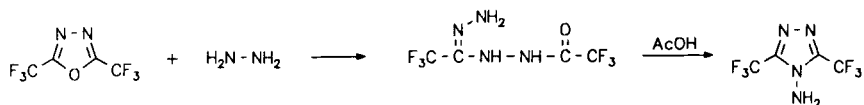
2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole undergoes ring cleavage on treatment with hydrazine; the open-chain 1-(*N*-aminotrifluoromethylimido)-2-trifluoroacetyl hydrazine is ring closed again on boiling with acetic acid in a 5-*exo-trig* process (89JOC1760). When primary aliphatic or aromatic amines are employed instead of hydrazine, 4-alkyl- and 4-aryl-



SCHEME 48



SCHEME 49



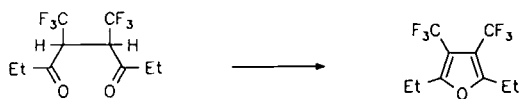
SCHEME 50

substituted 3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles are obtained (89JHC225) (Scheme 50).

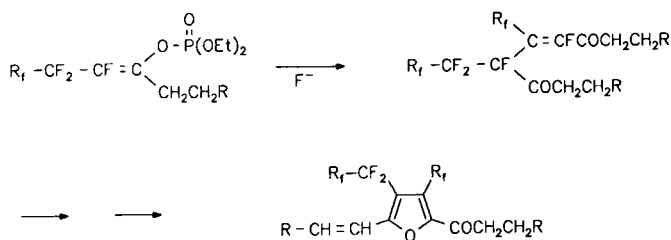
The adduct obtained from acetaldehyde and perfluoro-3,4-dimethylhex-3-ene on γ -irradiation was transformed thermally into a fluoroalkylated furan in the presence of tributylamine (80TL1891). 4,5-Bis(trifluoromethyl)octa-3,6-dione, the addition product of propionaldehyde to hexafluoro-2-butyne on γ -irradiation, yields 2,5-diethyl-3,4-bis(trifluoromethyl)furan on treatment with sulfuric acid (91JHC225) (Scheme 51).

1-Alkyl-1-perfluoroalkenylphosphates, which easily can be dephosphorylated in the presence of fluoride ions and triethylamine, undergo a 1,5 cyclocondensation reaction to give furan derivatives (87CL1621) (Scheme 52).

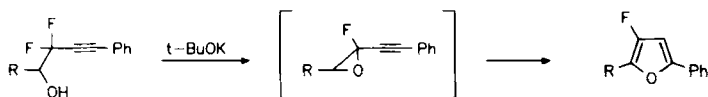
1-Decynyldi- and 1-Decynyltri-fluoromethyl ketoxime cyclize in 5-*endo-dig* processes to provide 3-difluoromethyl- and 3-trifluoromethyl-isoxazoles (89TL2049). A highly efficient, regiocontrolled synthesis for 3-fluorofurans proceeds via base-induced cyclization reaction of the Reformatzky adduct from bromodifluoromethyl phenylacetylene and aldehydes. An epoxide is suggested to be the intermediate of this reaction (91CC1134), but this cyclization can also be rationalized as a 5-*endo-dig* process. There are a significant number of examples of heterocyclic



SCHEME 51



SCHEME 52



SCHEME 53

syntheses known involving *endo* cyclization onto a triple bond. Although such reactions appear to be sterically unfavorable because of the linear nature of the triple bond, it is easy to distort the triple bond to achieve the required transition-state geometry (78JA6007; 79JA1340) (Scheme 53).

D. MISCELLANEOUS

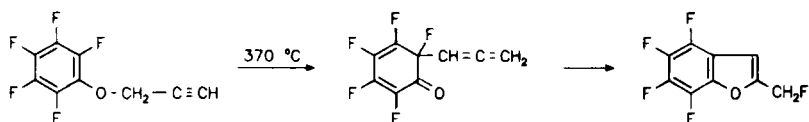
Pentafluorophenyl propargyl ether isomerizes in the gas phase on silica gel at 370°C to give 2-monofluoromethyl-4,5,6,7-tetrafluorobenzo[*b*]-furan [81JCS(P1)1417]. Via the same route, naphtho[2,1-*b*]furans [82JCS(P1)107, 82JFC(20)173] and 4,5,6,7-tetrafluoro-2,3-dihydro-2-methyl-1-benzothiophene [81JCS(P1)1659] can be synthesized (Scheme 54).

IV. Introduction of Fluorine, Polyfluoroalkyl, and Perfluoroalkyl Groups into Five-Membered Heterocycles via Cycloaddition Reactions

A. [3 + 2] CYCLOADDITION REACTIONS

The 1,3-dipolar cycloaddition is a general principle for the synthesis of five-membered heterocyclic systems with well-defined substitution patterns, and in many cases with great stereochemical control (84MI2). The “Woodward–Hoffmann Rules” provide the basis for mechanistic understanding [69AG(E)781; 79MI1], and the application of frontier orbital theory rationalizes the effects of substituents bonded to the 1,3-dipolar and dipolarophilic species on the rates and selectivities of [3 + 2] cycloaddition reactions (74PAC569; 76MI1).

The concept of the 1,3-dipolar cycloaddition is especially valuable for the construction of five-membered heterocyclic systems, substituted by



SCHEME 54

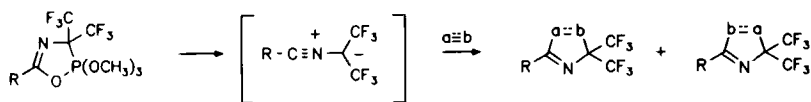
fluorine and/or short-chain perfluoroalkyl groups, because of the wide variety of 1,3-dipoles and dipolarophiles available. Since fluorine and fluorinated side chains can be introduced regioselectively into the 1,3-dipolar as well as into the dipolarophilic species (or into both of them), this synthetic principle is extremely flexible.

Incorporation of perfluoroalkyl groups into 1,3-dipoles usually increases reactivity, i.e. by lowering the energies of the frontier orbitals and reducing the LUMO 1,3-dipole/HOMO dipolarophile energy gap. On the other hand, when perfluoroalkyl and partially fluorinated substituents are directly bonded to the dipolarophile skeleton, cycloaddition reactions occur preferentially under HOMO 1,3-dipole/LUMO dipolarophile control. Furthermore, perfluoroalkyl groups often stabilize the newly formed ring systems.

1. Introduction of Fluorine-containing Substituents into Five-Membered Heterocycles via Fluoro-substituted 1,3-Dipoles

a. *Perfluoroalkyl-substituted 1,3-Dipoles of the Propargyl-Allenyl Type.* Trifluoromethyl-substituted (71CB3816; 73CB2863) and bis(trifluoromethyl)-substituted (72CB3814; 74CB1823; 79MI2) nitrile ylides have been generated via different routes and trapped by various dipolarophiles to yield trifluoromethyl- and bis(trifluoromethyl)-substituted five-membered ring systems containing one, two, or three heteroatoms [71CB1408; 78JFC(12)519; 83CL1463; 84MI3; 89HCA825; 91AX(C)1550] (Scheme 55).

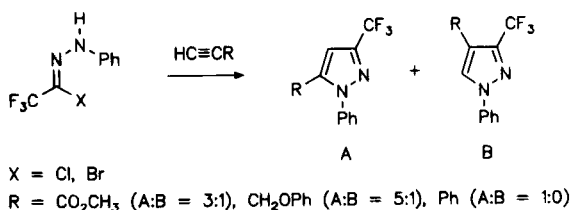
Likewise, trifluoromethyl-substituted nitrile imines, generated from 2,3-dihydro-3-phenyl-5-trifluoromethyl-2,2,2-trimethoxy-1,3,4-diaza-2-phospholes (84BCJ2689), or *N*-phenyltrifluoroacetohydrazonoyl bromide (82CL543; 83CL507; 85BCJ1841, 85JHC565; 86BCJ3901; 87MI1), and trifluoroacetonitrile oxide, generated *in situ* from hydroximoylchloride or bromide by base-induced 1,3-elimination (84JOC919; 86BCJ3901; 89CHE815), have been used as trifluoromethyl-containing building blocks to synthesize trifluoromethyl-substituted five-membered ring systems of the pyrazole, pyrazoline, isoxazole, isoxazoline, and 1,2,4-oxadiazole



R = CH(CH₃)₂, *t*-C₄H₉, 4-CH₃C₆H₄

a=b = H₃CO₂C-C≡C-CO₂CH₃, H₃C₈-C≡C-C₈H₅, H-C≡C-CO₂CH₃,
H₃CO₂C-CH=CH-CO₂CH₃, H₂C=CH-CO₂CH₃, H₂C=CH-C≡N

SCHEME 55



SCHEME 56

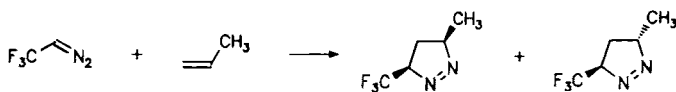
type (84BCJ2184; 85BCJ2061; 86BCJ2631, 86JHC1535; 87BCJ4480, 87JHC1391; 89CHE555) (Scheme 56).

In the absence of trapping reagents, trifluoroacetonitrile oxide dimerizes to give a trifluoromethyl-substituted furoxan or a 1,4-dioxo-2,5-diazine, depending on the identity of the 1,3-dipolar species.

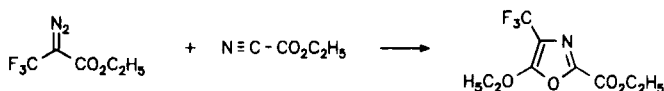
b. *Trifluoromethyl-Substituted Diazonium Betaines*. [3 + 2] cycloaddition reactions of trifluoromethyl-substituted diazoalkanes [68JCS(C)1507; 79JFC(13)147; 89JFC(45)323] and alkyl 3,3,3-trifluoro-2-diazopropionates (89CC607) have been described. Trifluoromethyldiazomethane was found to react with ethylene and regiospecifically with propene to give pyrazolines. In the latter case a 1 : 1.3 mixture of *cis*/*trans* isomers was obtained (Scheme 57).

The [3 + 2] cycloadduct formed on treatment of tetrakis(trifluoromethyl)-Dewar-thiophene with trifluoromethyl diazomethane isomerizes to give an annulated 3-trifluoromethyl-1*H*-2-pyrazoline in the presence of acids and bases. Sulfur can be removed from both compounds on reaction with triphenylphosphine (80JA6633).

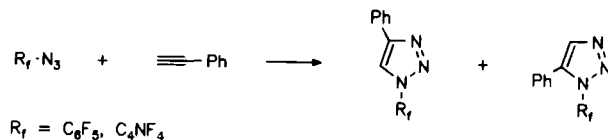
Photolytic (68CB302) or rhodium-catalyzed decomposition of alkyl 3,3,3-trifluoro-2-diazopropionates gives carbenes and carbene complexes, respectively, which exhibit an enormous synthetic potential. [3 + 2] cycloaddition reactions have been performed, e.g., with nitriles to give 4-trifluoromethyl-substituted oxazoles [90JOC3383; 91JFC(52)149] (Scheme 58).



SCHEME 57



SCHEME 58



SCHEME 59

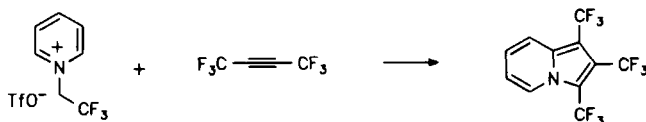
c. *Perfluoroaryl- and Perfluoroheteroaryl-substituted Azides.* Azides bearing electron-withdrawing groups add to olefins often with spontaneous loss of nitrogen (84MI6). 4-Azidotetrafluoropyridine adds at room temperature to norbornene as well as to dicyclopentadiene to give *exo*-aziridines; the intermediate triazoline could not be isolated [72JCS(P1)2964]. In contrast, pentafluorophenyl azide and tetrafluoro-4-azidopyridine add to phenylacetylene to yield both regioisomers [74JCS(P1)1365] (Scheme 59).

[3 + 2] cycloaddition of 2-aryl-5-azido-3-trifluoromethylthiazoles to dimethyl acetylenedicarboxylate occurs even at room temperature. Unsymmetrically substituted alkynes, such as propiolates, react to give two regioisomers [90ZN(B)1695].

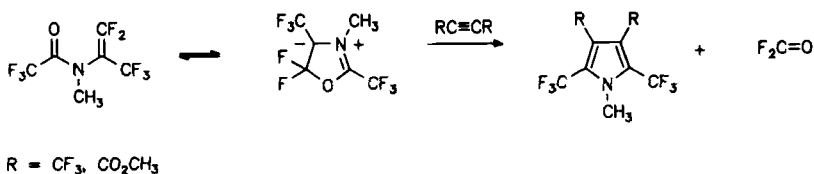
d. *Partially Fluorinated 1,3-Dipoles of the Allyl Type.* A general route to azomethine ylides employs proton abstraction from immonium salts with bases (84MI7). This concept was adapted to generate highly reactive partially fluorinated azomethine ylides. The [3 + 2] cycloadducts with alkynes are sensitive to oxidation and can be transformed into fluorinated indazolines [86JFC(34)275; 88JFC(38)289] (Scheme 60).

The indazolines themselves may be regarded as masked azomethine ylides and therefore are susceptible to further [3 + 2] cycloaddition reactions (59JOC582). *N*-Methyl-*N*-(2-perfluoropropenyl)trifluoroacetamide exists in a valence tautomeric equilibrium with a cyclic azomethine ylide, which can be trapped with various dipolarophiles. The [3 + 2] cycloadducts with alkynes rearomatize on cycloelimination of fluorophosgene to give trifluoromethyl-substituted pyrroles (89BAU1325) (Scheme 61).

Trifluoromethyl-substituted azomethine imines are intermediates of the "criss-cross" cycloaddition reaction [74AG(E)474; 76S349]. They are the most thoroughly investigated trifluoromethyl-substituted 1,3-dipoles. Hexafluoroacetone azine [73AG(E)502; 84JOU1646] reacts with two equivalents of terminal olefins [71JCS(C)2404] or alkynes (75TL1125) to



SCHEME 60



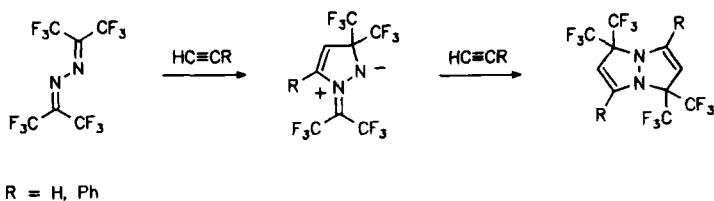
SCHEME 61

give 1,5-diazabicyclo[3.3.0]octanes and 1,5-diazabicyclo[3.3.0]octa-2,6-dienes, respectively (Scheme 62).

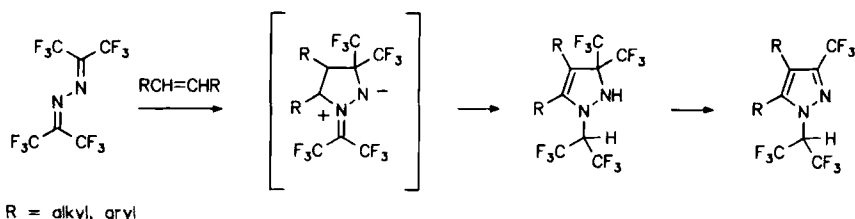
The criss-cross cycloaddition process consists of two separate [3 + 2] cycloaddition steps. In summary, it represents a 1,3/2,4 cycloaddition of multiple bond systems to the azine skeleton. The structure of the azomethine imine intermediate has been proved by X-ray structure analysis [74AG(E)475]. Ethylene [71JCS(C)2404], acetylene (75TL1125), many terminal alkyl-, aryl-, geminal dialkyl-, and diaryl-substituted alkenes [75CB1460, 75JCS(P1)538, 75JCS(P1)1902; 82JFC(19)589], dienes [75JCS(P1)1411], terminal alkyl- and aryl-substituted alkynes (75TL1125; 79CB2609), certain cyclic alkenes (79T389), vinyl ethers (82LA853), alkoxyacetylenes and ynamines (79LA133), acrylates (82LA845), and propiolates (79CB2609) react similarly. Under appropriate reaction conditions the intermediate azomethine imines can be isolated.

Based on this concept, a preparatively simple route to the previously unknown 1*H*-3-pyrazolines was developed. Olefins of type $\text{RCH}=\text{CHR}$ and hexafluoroacetone azine react to give azomethine imines, which subsequently are transformed in a series of prototropic shifts to give 1*H*-3-pyrazolines [75JCS(P1)538; 79T389]. The latter on heating with AIBN undergo fluoroform elimination with heteroaromatization to yield trifluoromethyl-substituted pyrazoles [82JFC(19)437] (Scheme 63).

An unexpected [1.4] migration of a trifluoromethyl group was observed when azomethine imines were synthesized from hexafluoroacetone azine and alkoxyalkynes. The rearrangement, which occurs at temperatures as low as 0°C , is probably a radical process and results in the formation of *N*-(perfluoro-*tert*-butyl)pyrazoles (79CC792). The formation of



SCHEME 62



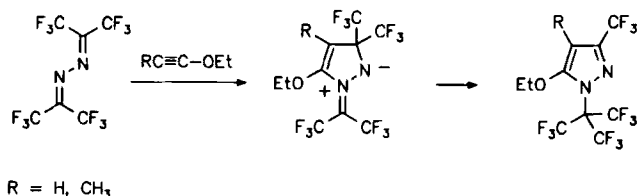
SCHEME 63

a perfluoro-tert-butyl group via trifluoromethyl group migration is without precedence (Scheme 64).

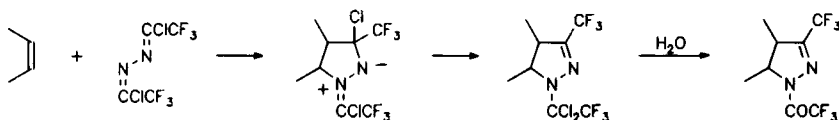
Azomethine imines obtained from 1,4-dichloro-1,4-bis(trifluoromethyl)azine and cycloalkenes or cycloalkadienes undergo [1,4] chlorotropy. Subsequent hydrolysis yields 1-trifluoroacetyl-3-trifluoromethyl-2-pyrazolines (93CC9) (Scheme 65).

Numerous [3+2] cycloaddition reactions have been performed with bis(trifluoromethyl)-substituted azomethine imines (79CB2609, 79LA133). Noteworthy is the [3+2] cycloaddition reaction with tetracyanoethylene, which adds across one of the nitrile functions instead of adding across the CC double bond. This is one of the rare examples of this type of periselectivity found in the case of tetracyanoethylene in [3+2] cycloaddition processes (76LA30).

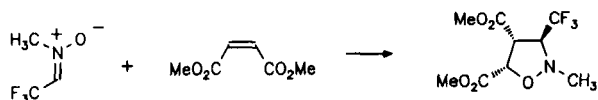
Since the criss-cross cycloaddition reaction is a sequence of two [3+2] cycloaddition steps, the reaction of hexafluoroacetone azine with α,ω -diolefins offers access to a new class of trifluoromethyl-substituted heterocyclic macromolecules. Polymers with interesting structures and properties become available by criss-cross polymerization (88M13; 89M12; 90M12).



SCHEME 64



SCHEME 65



SCHEME 66

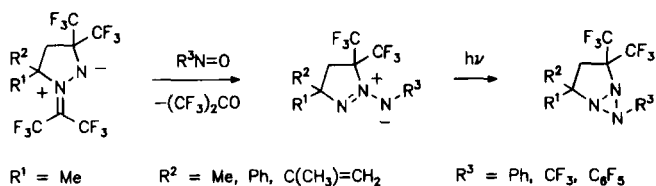
The “Diels–Alder” adduct isolated from the reaction of hexafluoroacetone azine and 2,3-dimethyl-1,3-butadiene at elevated temperatures [75JCS(P1)1411] in fact is the result of a two-step process, namely of a [3 + 2] cycloaddition reaction and a subsequent [3.2] sigmatropic rearrangement [82JFC(19)589].

Open-chain azines with multiple-bond systems do not react as 1,3-dienes but as 1,3-dipoles to give 1,3- and 1,3/2,4-cycloadducts, respectively. This is probably due to the lone pair/lone pair repulsion, which makes the *s-cis* conformation unfavorable. “Azines appear to behave as if the diene π -bonds are orthogonal to each other, so that the system has two orthogonal azomethine imine moieties” (79MI5). Consequently, 1,4 cycloaddition reactions with azines are only feasible when the azine skeleton is incorporated into a ring system [59JA4342; 78JCS(P1)378; 86AP690; 88CPB3354].

Trifluoromethyl-substituted nitrones have been prepared [78JFC(12)153; 88JFC(39)39, 88MI2; 89JHC381] and used as building blocks for five-membered ring synthesis (Scheme 66).

Trifluoromethyl-substituted azimines are surprisingly stable compounds. They are formed by 1,3-dipole metathesis from trifluoromethyl-substituted azomethine imines and certain nitroso compounds [78JFC(11)567; 82CZ408]. Photolytically they can be ring closed to give the first representatives of triaziridines completely stable at room temperature. On heating above 80–100°C the trifluoromethyl-substituted triaziridines undergo ring opening to give back the starting azimines [85AG(E)341] (Scheme 67).

When pentafluoronitroacetone and 2,3-dimethyl-1,3-butadiene are reacted, a two-step procedure can be observed. In the [4 + 2] cycloadduct initially formed the nitro group is suitably placed to undergo an intramolecular [3 + 2] cycloaddition reaction with the newly formed CC double bond



SCHEME 67

of the dihydropyrane ring to form a caged product (68BAU357; 82BAU536).

2. *Introduction of Fluorine-containing Substituents into Five-Membered Heterocycles via Dipolarophiles*

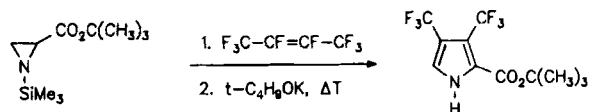
Perfluorinated and partially fluorinated substituents directly bonded to multiple bonds of dipolarophiles lower the energies of the frontier orbitals. Consequently, this class of dipolarophiles is highly reactive in HOMO 1,3-dipole/LUMO dipolarophile controlled [3 + 2] cycloaddition reactions. Since 1,3-dipoles (84MI1) and fluorosubstituted olefins, alkynes, carbonyl and thiocarbonyl compounds, imines, nitriles, and nitroso compounds (70MI2; 73MI2; 76MI4) are readily available, this strategy offers a general and preparatively simple route to fluorinated five-membered heterocyclic systems.

a. *Via Fluoroolefins.* Fluoroolefins should be susceptible to reaction with all kinds of 1,3-dipoles. The [3 + 2] cycloadducts initially formed often undergo heteroaromatization by HF elimination or cycloreversion reactions. Hexakis(trifluoromethyl)phosphabarrelene and diazomethane yield 4,5-bis(trifluoromethyl)pyrazole quantitatively. A [3 + 2] cycloadduct is the intermediate in this process (77TL867).

Perfluoropropene (66JOC789) and perfluoroisobutene (86BAU231) add benzyl azide to give [3 + 2] adducts, which have been tentatively ascribed a 1,2,3-triazol-2-ine structure. Hexafluorobicyclo[2.2.0]hexa-2,5-diene (hexafluoro-Dewar-benzene) and phenyl azide at 34°C react slowly to give a mixture of *exo*-triazoline-*exo*-aziridine and *exo, exo-trans* bistriazoline [73JCS(P1)1798]. Azides already add at room temperature across the CC double bond of tetrakis(trifluoromethyl)-5-thiabicyclo[2.1.0]-2-pentene [tetrakis(trifluoromethyl)-Dewar-thiophene]. On photolysis the newly formed triazoline is transformed into an aziridine ring system; this tricyclic system subsequently can be desulfurized. Via this route tetrakis(trifluoromethyl)-substituted Dewar-pyrroles become readily accessible (77JA7350; 80JOC2962).

The [3 + 2] cycloadduct obtained from tetrakis(trifluoromethyl)diphosphabenzvalene and phenyl azide undergoes ring contraction on photolysis to give the corresponding aziridine, whereas during chromatography on silica gel a cycloreversion reaction with formation of 4,5-bis(trifluoromethyl)-1,2,3-triazole was observed (80JOC4683).

Aziridines on thermolysis and photolysis give azomethine ylides, which can be trapped by fluoroolefins (76CJC218). In the case of the [3 + 2] cycloadduct of 1-trimethylsilyl-2-tert-butoxycarbonyl aziridine and per-

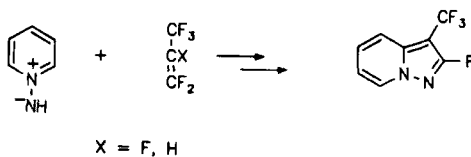


SCHEME 68

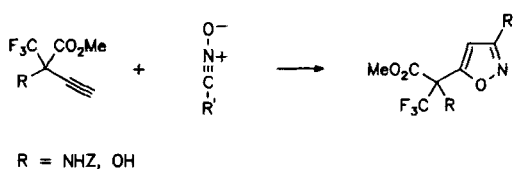
fluoropropene or perfluoro-2-butene (autoclave, 160°C), heteroaromatization was achieved on treatment with potassium-*tert*-butoxide at elevated temperatures (82S313) (Scheme 68).

Pyrrolo[1,2-*a*]pyridines result from the reaction of pyridinium methyldes and perfluoropropene [85JCR(S)33]. Azomethine imines, like *N*-iminopyridinium and *N*-iminochinolinium ylides, react with perfluoropropene, 2*H*-pentafluoropropene, and perfluoro-2-butene analogously to give annulated pyrazoles [80JFC(15)179]. Again the [3 + 2] cycloadducts initially formed eliminate HF and/or F_2 . The $-\text{N}=\text{CF}-\text{C}(\text{CF}_3)=$ moiety incorporated into the ring system is of special preparative value because the single fluorine atom easily can be substituted by a wide variety of nucleophiles (88S194, 88S199) (Scheme 69).

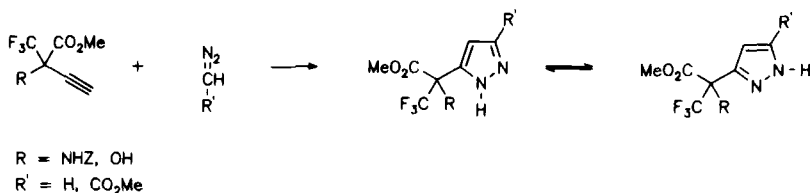
b. *Via Fluorinated Alkynes.* Nitrile oxides (84MI4) and 1-aryl-3,3,3-trifluoropropynes (89S331) do not react regioselectively, with 5-aryl-4-trifluoromethylisoxazoles always being the main products. In contrast, 5-substituted isoxazoles were obtained exclusively on reaction with terminal alkynes, like α -trifluoromethyl-substituted alkynyl amino and alkynyl hydroxy acid esters. These heterocyclic 3,3,3-trifluoroalanine and 3,3,3-trifluorolactic acid derivatives are interesting candidates for peptide modification (92LA947) (Scheme 70).



SCHEME 69



SCHEME 70



SCHEME 71

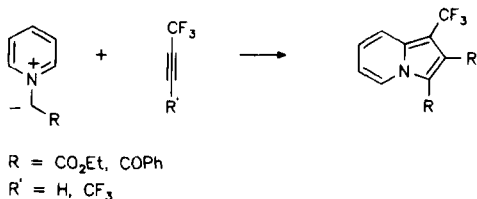
A spiro adduct is the result of the reaction of diazofluorene and perfluoro-2-butyne (72AG(E)224, 72TL3479; 74CB2027). With diazomethane and ethyl diazoacetate the above-mentioned trifluoromethyl-substituted alkynylamino and alkynyl hydroxy acid esters give a single [3 + 2] cycloadduct, namely the 2-(3-pyrazolyl)-3,3,3-trifluoroalanine and the 2-(3-pyrazolyl)-3,3,3-trifluorolactic acid derivatives, respectively (92LA947) (Scheme 71).

Azides rapidly react with electron-poor alkynes to give 1,2,3-triazoles (84MI5). A series of structurally different fluorosubstituted alkynes, like perfluoro-2-butyne (66JOC789), 1-aryl-3,3,3-trifluoropropynes [91JFC(55)199], 4,5-dichloro-1,1,1,6,6,6-hexafluorohex-4-en-2-yne, perfluoro-2,4-hexadiyne (66JOC3292), and 2-ethynyl-3,3,3-trifluoroalanines (92LA947) react analogously to give fluoro-substituted 1,2,3-triazolines.

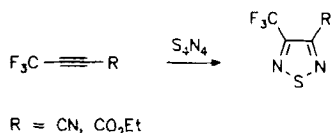
The [3 + 2] cycloadducts from pyridinium methylides and perfluoro-2-butyne as well as 3,3,3-trifluoropropyne in the presence of sodium hydride are spontaneously transformed into the trifluoromethyl-substituted indolizines [91JFC(51)407] (Scheme 72).

Hexafluoro-2-butyne and carbon disulfide react to give the tetrakis-(trifluoromethyl)tetrathiafulvalene quantitatively only in the presence of trifluoroacetic acid (70JA1412; 73JA4379). The carbene initially formed is protonated; the 1,3-dithiolium ion subsequently combines with the nucleophilic carbene to give the trifluoromethyl-substituted tetrathiafulvalene.

A preparatively and mechanistically interesting synthesis of trifluoromethyl-substituted thiadiazoles from trifluoromethyl-substituted alkynes and tetrasulfur tetranitride has been described [87JCS(P1)1579, 87JCS(P1)1585] (Scheme 73).



SCHEME 72



SCHEME 73

c. *Via Polyfluoroalkyl- and Perfluoroalkyl-substituted Carbonyl Compounds.* Nitrile ylides generated from 2*H*-azirines on photoysis add to C=O double bonds of trifluoromethyl ketones and methyl trifluoroacetate to yield 5-trifluoromethyl-substituted 3-oxazolines (75HCA1739; 83HCA262; 84MI3).

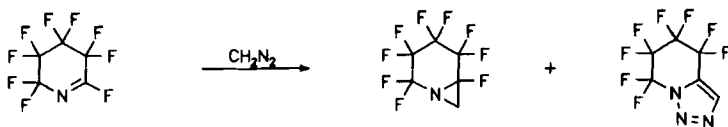
Diazoalkanes react with carbonyl compounds, usually under very mild conditions, to give oxiranes and ketones. The reaction has been interpreted as a nucleophilic attack of the diazoalkane on the carbonyl group to yield diazonium betaines of 1,2,3-oxadiazol-2-ines as reaction intermediates, which generally are too unstable to be isolated. Aromatic diazo compounds react readily with partially fluorinated and perfluorinated ketones to give 1,3,4-oxadiazol-3-ines in high yield. However, above 25°C the aryloxadiazolines lose nitrogen to give epoxides (78JA4260; 86JOC2366).

d. *Via Polyfluoroalkyl- and Perfluoroalkyl-substituted Imines.* *N*-Benzenesulfonyl imines of hexafluoroacetone readily react with nitrile oxides (79JOU2008; 81ZVK350; 82BAU1663; 86ZVK112), oxiranes, and thiiranes to give 1,2,4-oxadiazol-2-ines, oxazolidines and thiazolidines, respectively (Scheme 74).

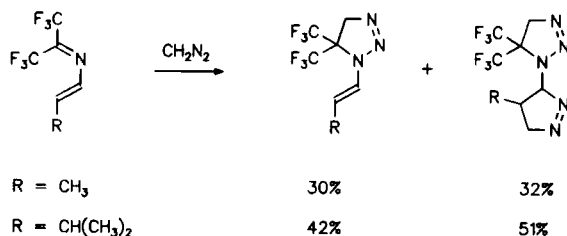
The perfluorinated six-membered azomethine imine and diazomethane react at temperatures as low as -80°C to form the aziridine together with the [3 + 2] cycloadduct, which stabilizes on elimination of HF to give the annulated 1,2,3-triazoline [77JFC(10)553] (Scheme 75).



SCHEME 74



SCHEME 75



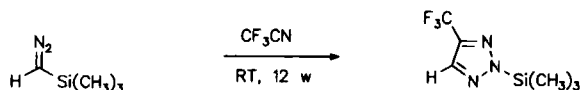
SCHEME 76

Halogenated and halogenoalkyl-substituted imines react with diazoalkanes under very mild conditions and preferentially afford aziridines [72LA(757)9; 84RCR238]. Diazonium betaines have been considered to be intermediates of these reactions (64JOC3049; 71T51). On reaction of diazomethane with certain imines of hexafluoroacetone (67BAU695; 84RCR238), 1,1-bis(trifluoromethyl)-2-azabut-1,3-dienes [72LA(757)9], or hexafluoroacetone azine [76JFC(7)471], stable [3 + 2] cycloadducts have been obtained. The latter two hetero-1,3-dienes are capable of adding two molecules of diazomethane (Scheme 76).

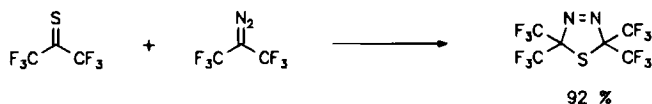
e. *Via Perfluoroalkyl Nitriles.* Perfluoroalkyl-substituted nitriles react with various 1,3-dipoles, such as nitrile ylides (76HCA1018), diazoalkanes [73JCS(D)483], azides (62JOC2085; 79JOU1677, 79JOU2009), azomethine ylides [81H1223; 83JFC(22)589; 86JCS(P1)1769, 86JFC(34)275; 91JFC(51)407], and azomethine imines [80JFC(15)179; 82JFC(20)373] to give stable five-membered ring systems. Nonaromatic [3 + 2] cycloadducts obtained from perfluoroalkyl nitriles often exhibit tendency to aromatize on subsequent oxidation, elimination, or rearrangement (Scheme 77).

3. Introduction of Perfluorinated and Polyfluorinated Substituents via 1,3-Dipoles and Dipolarophiles

Fluoro-containing substituents can be introduced regioselectively into five-membered heterocycles by using the enormous synthetic potential of the [3 + 2] cycloaddition reaction via the 1,3-dipolar or/and dipolarophilic species. In the latter case fully perfluoroalkyl-substituted five-membered heterocycles become available.



SCHEME 77



SCHEME 78

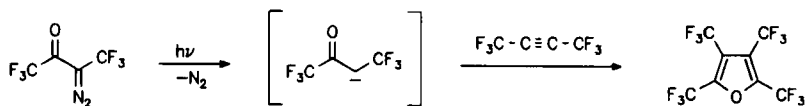
Perfluoro-2-diazopropane and hexafluorothioacetone react at temperatures as low as -30°C to give the tetrakis(trifluoromethyl)-substituted 1,3,4-thiadiazoline in nearly quantitative yield (69JOC3201) (Scheme 78).

Pyridinium (trifluoroacetyl)methylide forms [3 + 2] cycloadducts with a wide variety of perfluorinated and partially fluorinated olefins, alkynes, and nitriles [86JFC(34)275]. Photolysis of a mixture of hexafluoro-3-diazobutan-2-one and perfluoro-2-butyne in the gas phase results in the formation of tetrakis(trifluoromethyl)furan; a ketocarbene is the key intermediate of this reaction sequence (87JOC2680) (Scheme 79).

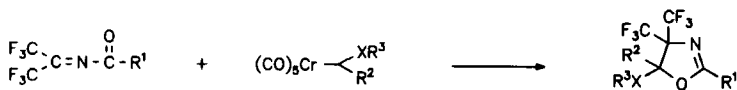
When 1,2,3-thiadiazoles are photolyzed in the gas phase in the presence of hexafluoro-2-butyne, 2,3-bis(trifluoromethyl)thiophenes are formed; a plausible intermediate for this process seems to be a thiirine (74CRV431).

B. SYNTHESIS OF PERFLUOROALKYL-SUBSTITUTED FIVE-MEMBERED HETEROCYCLES VIA [4 + 1] CYCLOADDITION REACTIONS

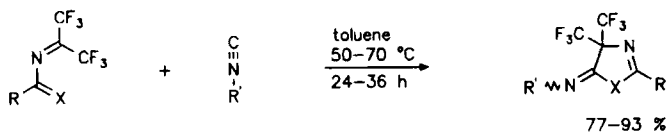
Bis(trifluoromethyl)-substituted hetero-1,3-dienes are excellent traps for single-ring atom species, even when these are short-lived. They add electron-rich and electron-poor carbenes [77CZ402; 79BAU1688; 82JFC(20)813], carbene complexes (73CB1581), carbene analogues (SnCl_2 , $\text{Sn}(\text{C}_5\text{H}_5)_2$, GeCl_2) [88S189; 90JFC(46)105], P(III) species (71CB1826; 77ZVK228; 79MI6), isonitriles [82JFC(20)813], etc., to give trifluoromethyl-substituted five-membered heterocycles (Scheme 80).



SCHEME 79



SCHEME 80



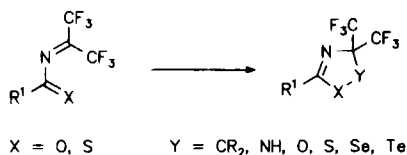
SCHEME 81

Trimethylsilyl cyanide and certain cyanofornates add to give five-membered ring systems having the same structure as the isonitrile adducts (84CZ209; 88S44) (Scheme 81).

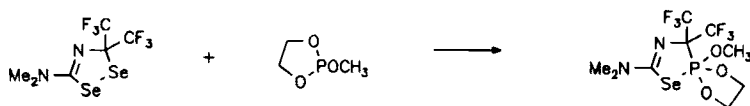
[4 + 1] cycloadducts are also formed on transfer of one-ring atom fragments from reactive species to bis(trifluoromethyl)-substituted hetero-1,3-dienes: CR_2 from diazo alkanes (67JGU2355), NH from hydrazoic acid [87JFC(36)329]; O from peroxy acids [87JFC(37)53]; S from phosphorus pentasulfide, Lawesson's reagent (77CB2114), and S_8 (86CZ87); Se from phosphorus pentaselenide (80CB2699) and Se_8 (86CZ87); and Te from antimony telluride (77CC80). When oxygen is in a terminal position of the hetero-1,3-diene, a replacement of oxygen by chalcogenes is often observed during formation of the five-membered ring (Scheme 82).

Five-membered heterocycles with two vicinal chalcogen atoms in the ring system can be used as stable precursors for sulfur as well as for selenium-containing hetero-1,3-dienes in cycloaddition reactions. Consequently, 3*H*-1,2,4-thiaselenazoles have been used for the *in situ* formation of 4,4-bis(trifluoromethyl)-1-thia-3-azabuta-1,3-dienes, which exist at room temperature only as 4,4-bis(trifluoromethyl)-2*H*-1,3-thiazetes. This strategy was applied to the synthesis of the first stable selenophosphorane from bis(trifluoromethyl)-substituted 3*H*-diselenazol and 2-methoxy-1,3,2-dioxaphospholan [78AG(E)774] (Scheme 83).

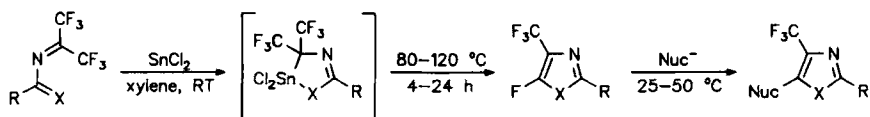
From all [4 + 1] cycloadducts generated from 4,4-bis(trifluoromethyl)-substituted hetero-1,3-dienes of type $(\text{F}_3\text{C})_2\text{C}=\text{N}-\text{C}(\text{R})=\text{X}$ ($\text{X} = \text{O}, \text{S}$,



SCHEME 82



SCHEME 83

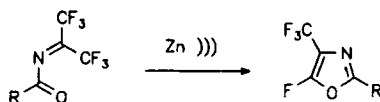


SCHEME 84

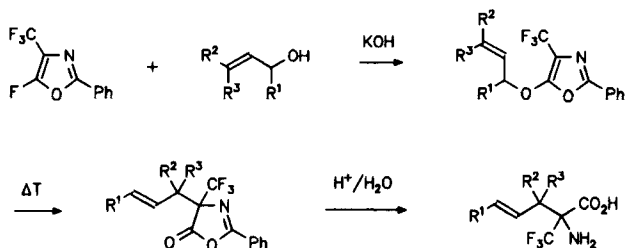
NR'), the tin heterocycles exhibit the most promising preparative potential [78TL5003; 82CB2494; 88S189, 88S199; 90JFC(46)105; 92CC348]. On heating, they undergo a heterolytic ring cleavage, fluoride elimination, and fragmentation with loss of the tin moiety to give a heteropentadienyl anion, which undergoes 1,5-electrocyclization and fluoride elimination with heteroaromatization. This reaction sequence can be performed as a "one pot procedure" in good yields (Scheme 84).

With certain 4,4-bis(trifluoromethyl)-3-aza-1-oxabutadienes this transformation can be achieved on heating with metals (91CZ253), especially zinc (89CHE1418) or with zinc/ultrasound (91CZ253). The fluorine atom at C—5 can be readily replaced by various nucleophiles (88S194). Via this route, 4-trifluoromethyl-1,3-oxazoles, -1,3-thiazoles, and -imidazoles can be introduced into many compounds of biological interest (Scheme 85).

A wide variety of α -trifluoromethyl-substituted amino acids are now available from the reaction of 5-fluoro-4-trifluoromethyl-1,3-oxazoles with allylic alcohols and benzyl alcohols. The reaction sequence involves a low-temperature Claisen rearrangement or a radical 1,3-benzyl shift from oxygen to carbon, respectively [88AG(E)848; 89S850] (Scheme 86).

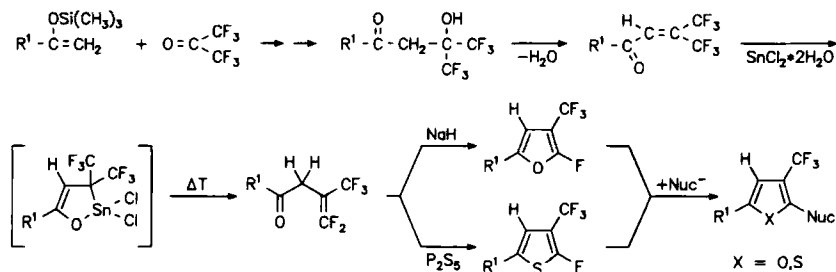


SCHEME 85



R¹-R³ = H, Me, Et, Pr

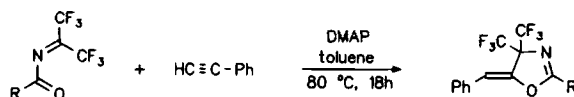
SCHEME 86



SCHEME 87

The [4 + 1] cycloadducts formed from 4,4-bis(trifluoromethyl)-1-oxabuta-1,3-dienes (92JPR219) and tin(II)-chloride are transformed on heating into 4,4-difluoro-3-trifluoromethylbut-3-en-1-ones, which on treatment with sodium hydride yield 2-fluoro-3-trifluoromethylfurans (92CC348). When heated with phosphorus pentasulfide, 1-aryl-4,4-difluoro-3-trifluoromethylbut-3-en-1-ones give 2-fluoro-3-trifluoromethylthiophenes. The fluorine atom at C—2 of the furans and thiophenes can readily be substituted by a wide variety of nucleophiles (92JPR311). This reaction sequence represents a preparatively useful method for the selective introduction of biologically relevant substituents into the C—2 position of 3-trifluoromethyl-substituted furans and thiophenes (Scheme 87).

4,4-Bis(trifluoromethyl)-substituted hetero-1,3-dienes and alkynes react to give open-chain trifluoromethyl-substituted *N*-propargylic amides, 4*H*-1,3-oxazines, and, surprisingly, 2-oxazolines [83CZ271; 89ZN(B)1298]. The formation of 2-oxazolines is one of the rare examples where only one carbon atom of an acetylene moiety is incorporated into the newly formed ring system in a cycloaddition process. The selectivity of this reaction can be controlled efficiently in favor of the five-membered ring system by adding one equivalent of 4-dimethylaminopyridine. The five-membered ring now becomes the main or the exclusive product. The value of 4-dimethylaminopyridine and similar species for manipulating periselectivity and regioselectivity in polar cycloaddition reactions was recognized only recently [89ZN(B)1298] (Scheme 88).



SCHEME 88

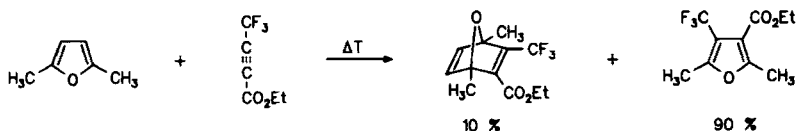
C. INTRODUCTION OF PERFLUOROALKYL GROUPS INTO FIVE-MEMBERED HETEROCYCLES VIA DIELS–ALDER/RETRO DIELS–ALDER REACTIONS

Five-membered heteroaromatic systems that possess an electron-deficient azadiene substructure, e.g., oxazoles and thiazoles, are suitable for participation in Diels–Alder reactions with inverse electron-demand [49JA3062; 59JA4342; 62AG(E)329]. The introduction of strongly electron-donating substituents in many cases is sufficient to overcome the electron-deficient nature of the azadiene moiety and permits normal HOMO diene/LUMO dienophile controlled Diels–Alder reactions (87MI6).

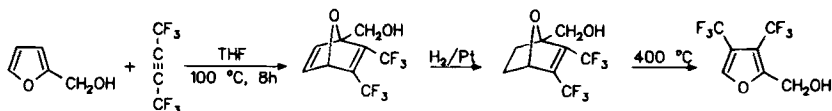
Acetylenic dienophiles react with oxazoles to provide furans, which arise from the retro Diels–Alder reaction with loss of RCN from the initially formed alkyne/oxazole Diels–Alder adduct. Olefinic dienophiles and oxazoles react to give pyridine derivatives resulting from a fragmentation of the initial [4 + 2] cycloadducts with subsequent aromatization.

Since perfluoroalkyl-substituted olefins and alkynes possess low-lying frontier orbitals, [4 + 2] cycloaddition reactions to oxazoles and thiazoles without strongly electron-donating substituents are unfavorable. On the other hand, five-membered heteroaromatic compounds possessing an electron-rich diene substructure, like furans, thiophenes, and pyrroles, should be able to add perfluoroalkyl-substituted olefins as well as alkynes in a normal Diels–Alder process. A reaction sequence consisting of a Diels–Alder reaction with perfluoroalkyl-substituted alkynes as dienophile, and a subsequent retro-Diels–Alder process of the cycloadduct initially formed, represents a preparatively valuable method for regioselective introduction of perfluoroalkyl groups into five-membered heteroaromatic systems.

Perfluoroalkyl-substituted propynoates and furans react to give Diels–Alder adducts. The success of the subsequent retro process depends on the substitution pattern of the furan ring system. The adducts of unsubstituted furan are thermally relatively stable, whereas the [4 + 2] cycloadducts of 2,5-dimethylfuran readily undergo a thermally induced retro-Diels–Alder reaction to give the 3-trifluoromethylfuran in high yield [91JFC(53)285] (Scheme 89).



SCHEME 89



SCHEME 90

The thermally stable furan adducts undergo a second Diels–Alder reaction with tetraphenylcyclopentadienone. The tetracyclic product obtained turns out to be thermolabile and breaks down on heating to give the trifluoromethyl-substituted furan together with 1,2,3,4-tetraphenylbenzene and carbon monoxide [91JFC(53)297].

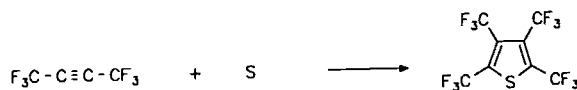
The cycloadducts formed on reaction of hexafluoro-2-butyne and 2-substituted furans can be hydrogenated selectively at the unsubstituted carbon double bond. On flash thermolysis at 400°C, these products undergo retro-Diels–Alder reaction to give 3,4-bis(trifluoromethyl)-substituted furans [91JFC(54)249]. A thermally stable [4+2] cycloadduct is obtained on heating hexafluoro-2-butyne and 3,4-bis(trifluoromethyl)-furan; the retro reaction occurs on photolysis (92JHC113) (Scheme 90).

This concept can also be applied for the synthesis of 3-perfluoroalkyl- and 3,4-bis(perfluoroalkyl)-substituted pyrroles [82JOC4779; 91JFC(53)-285]. The Diels–Alder adduct from *N*-(tert-butoxycarbonyl)pyrrole and perfluoro-2-butyne exhibits remarkable thermal stability, but after a second [4+2] addition of 2,4,6-trimethylbenzonitrile oxide the newly formed adduct is capable of a retro-Diels–Alder reaction, giving 3,4-bis(trifluoromethyl)pyrroles (82S313).

D. INTRODUCTION OF PERFLUOROALKYL GROUPS INTO FIVE-MEMBERED HETEROCYCLES VIA [2+2+1] CYCLOADDITION REACTIONS

Few examples of cycloaddition reactions of the type [2+2+1] where fluorosubstituted compounds are participating are known. Perfluoro-2-butyne and elemental sulfur react to give tetrakis(trifluoromethyl)thiophene [84JFC(25)47]. Analogously, a mixture of tetrakis(trifluoromethylthio)thiophene, 2,3,4-tris(trifluoromethylthio)-5-trifluoromethylthiophene, and tetrakis(trifluoromethylthio)-1,2-dithiin was obtained from bis(trifluoromethylthio)acetylene and sulfur at 170°C (85JHC1631) (Scheme 91).

Treatment of hexafluoroacetone with certain P(III) species results in the formation of five-membered ring systems via reductive CC coupling of two molecules of hexafluoroacetone [78CB890, 78CB2077; 79CB2380;



SCHEME 91

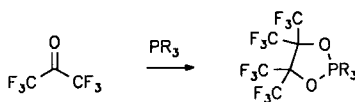
81BAU1344; 83CJC2264; 87JGU1708; 88ZN(B)196; 89CB1465; 90JFC-(48)99] (Scheme 92).

E. SYNTHESIS OF PERFLUOROALKYL-SUBSTITUTED FIVE-MEMBERED HETEROCYCLES VIA 1,5-ELECTROCYCLIZATION REACTIONS

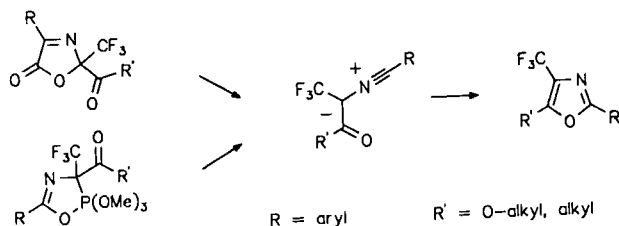
1,5-Electrocyclization reactions of perfluoroalkyl-substituted conjugated 1,3-dipoles (1,5-dipoles) and of heteropentadienyl anions and subsequent elimination with aromatization offer an elegant method for the selective introduction of perfluoroalkyl groups into five-membered heteroaromatic systems [79JCS(P1)214].

4-Trifluoromethyl-1,3-oxazoles are formed on heating 2-trifluoromethyl-2-acyl-2*H*-oxazol-5-ones (71CB1408) as well as 3-trifluoromethyl-3-alkoxycarbonyl-2,2,2-trimethoxy-5-phenyl-2,3-dihydro-1,4,2-oxazaphospholes (89CZ243). Both reaction sequences include a thermally induced [3 + 2] cycloreversion reaction and a 1,5-electrocyclization of the conjugated 1,3-dipolar species initially formed (Scheme 93).

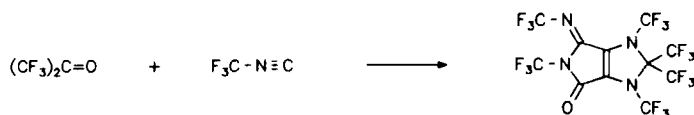
Tetrakis(trifluoromethyl)furan was obtained in nearly quantitative yield from 3-trifluoroacetyl-1,2,3-tris(trifluoromethyl)cyclopropene on heating in a Pyrex ampoule to 250°C in the presence of bromine (78TL1015).



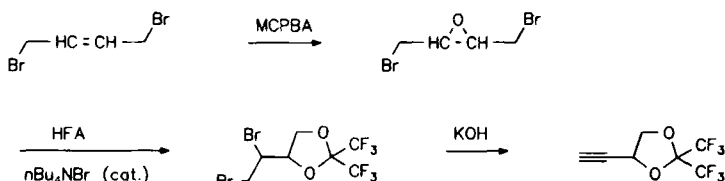
SCHEME 92



SCHEME 93



SCHEME 94



SCHEME 95

F. MISCELLANEOUS

Hexafluoroacetone and trifluoromethyl isocyanide react in an unexpected way to provide a bicyclic five-membered ring system [87AG(E)921] (Scheme 94).

2,2-Bis(trifluoromethyl)-4,5-difluoro-1,3-dioxole represents the monomer of a new family of amorphous fluoropolymers (Teflon AF, DuPont) with unusual properties [89JFC(45)100]. Novel fluorinated 2,2-bis(trifluoromethyl)dioxolanes containing alkyne groups have been synthesized from hexafluoroacetone and propargylic alcohol, bromomethyloxirane, or 1,2-bis(bromomethyl)oxirane [90MI1; 91JFC(52)159] (Scheme 95).

2-Pentafluoro-2-(2,2,2-trifluoro-1-trifluoromethylethyl)-1,3-dioxolanes exhibit electrical properties that make them useful as electrical insulating oils [86JAP(K)61-183281].

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Thiopyrylium, Selenopyrylium, and Telluropirylium Salts

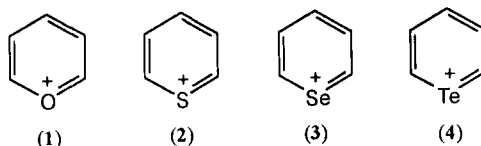
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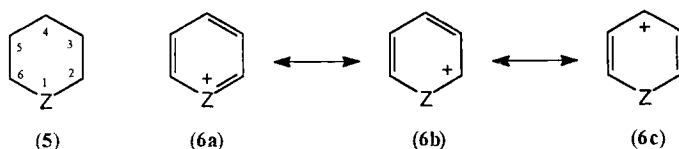
I. Introduction and Nomenclature

Pyrylium (1) and its chalcogen analogs, thiopyrylium (2), selenopyrylium (3), and telluropirylium (4), are the parent structures of an important class of six-membered heteroaromatic cations.



The term pyrylium is a well-established trivial name and is used in IUPAC nomenclature. The name may be modified by the prefixes thio, seleno, and telluro to denote replacement of oxygen by sulfur, selenium, and tellurium, respectively. The prefixes thia, selena, and tellura, although widely used, especially in the oldest literature, are not recommended by IUPAC because they indicate replacement of carbon. Other names for structures 2–4, derived from the extended Hantzsch–Widman system, are thiinium, seleninium, and tellurinium, respectively. However, according to the IUPAC rules for cations, the correctness of the suffix “ium” is questionable. The suffix “ylum,” used by some authors (79MI1; 83HCA2165), would be more accurate, since cation 2, for example, formally derives from a thiin, i.e., a thiopyran, by removal of hydride. Replacement nomenclature, according to which structures 2–4 would be named thionia-, selenonia-, and telluroniabenzene, is hardly used. *Chemical Abstracts* indicates structure 2 as thiopyrylium, and structures 3 and 4 as seleninium and tellurinium, respectively.

The chalcogenopyrylium ring is numbered as shown in formula 5. Positions 2 and 6 may also be denoted by α , positions 3 and 5 by β , and position 4 by γ . The anion has been left out in the formula pictures if it has no special influence on the chemical or physical properties of the chalcogenopyrylium ion. In most cases, however, the anion is a nonnucleophilic one, such as ClO_4^- , BF_4^- , or PF_6^- .



Chalcogenopyrylium ions have a marked carbocationic character illustrated by resonance structures 6b–6c, which suggest pronounced electrophilic reactivity of α and γ positions. Indeed most reactions occur through

a nucleophilic attack in position α and/or γ to give the corresponding *2H*- and/or *4H*-chalcogenopyrans. Whereas the reactivity of selenopyrylium and telluropyrilium salts is still almost unexplored, that of thiopyrylium salts has been investigated, although not as deeply as that of pyrylium salts. Generally speaking, the reactivity of thiopyrylium salts resembles that of pyrylium salts with two notable differences, namely the lesser tendency of *2H* adducts, formed on nucleophilic attack, to undergo ring opening and the ability of sulfur to accommodate more than eight electrons in its valence shell, leading, in some cases, to the formation of thiabenzene derivatives.

The chemistry of pyrylium salts has been covered in several excellent reviews [for leading references, see 82AHC(S)1; 92HOU755]. In contrast, except for some chapters found in monographs (76M11; 81M11) and in special articles appearing in less commonly used languages (70M11; 74M11; 75KGS147; 81Y GK1; 87M11), no exhaustive review on the other chalcogenopyrylium salts is available. The present review is an attempt to discuss the literature covered by *Chemical Abstracts* up to Vol. 117 (1992). Derivatives in which the chalcogenopyrylium ring is fused with an aromatic ring, such as thiochromenylium, thioflavylium, and thioxanthylum, and the corresponding seleno and telluro analogs, are not covered. Derivatives with exocyclic double bonds are also not covered, unless they are involved in processes (protonation, alkylation, etc.) yielding chalcogenopyrylium ions.

II. Structure and Physical Properties

A. THEORETICAL CALCULATIONS

Thiopyrylium cations have been the subject of a wide variety of theoretical investigations spanning the complete range of sophistication from simple Hückel (HMO) theory to *ab initio* calculations. The earliest HMO treatments of thiopyrylium ion were carried out by Czechoslovak authors (59CCC1608; 61TL632; 63CCC1117; 65CCC3016) using either the Longuet-Higgins *d*-orbital model or the standard *p*-orbital model for sulfur atom. The two models lead to the same predictions about the reactivity of thiopyrylium ion (63CCC1117). Early HMO studies on heterocyclic sulfur compounds, among which was the thiopyrylium ion, have been reviewed (65AHC1; 67ZC209).

A satisfactory linear relationship has been found to exist between the pK_{R^+} values of a series of conjugated carbocations, including thiopyrylium (2), and their π -electron localization energies calculated by HMO

(64JA5630). The apparent increased stability of the sulfur-containing cations has been ascribed to a lower stability of their corresponding alcohols. The obtained pK_R^+ value of the unsubstituted thiopyrylium ion, however, has been questioned (Section IV,C,3).

The long-wavelength electronic absorption frequencies of the thiopyrylium ion and a number of polynuclear benzologs have been correlated with transition energies calculated by HMO using the standard model for sulfur. The values of sulfur parameters have been optimized ($h_s = 0.9$ and $k_{CS} = 0.6$) to give the best linear correlation (67JOC444). An analogous good correlation has been found in the case of selenopyrylium cations using the parameters $h_{Se} = 1$ and $k_{CSe} = 0.7$ (76JOC1474). Although the application of HMO to charged systems has been criticized (69MI1), a linear relation between the HMO transition energies of the above thiopyrylium series and those calculated by Pariser–Parr–Pople (PPP) method with configuration interaction (CI) has been found, thus justifying HMO as a means of estimating transition energies in the case of thiopyrylium derivatives (68JPC3975). A fairly good linear correlation has been found between ^{13}C chemical shifts and net π -charges calculated by HMO (slope = 202 ppm/e) for a series of phenylthiopyrylium cations (84T3549). Correlations between HMO energy levels and redox potentials, as well as between HMO energy gaps and transition energies, have been established for a series of γ -thio- and γ -seleno-pyrylocyanines (84MI1).

The absorption spectra of the thiopyrylium cation and derived condensed ring systems are very well reproduced by PPP theory. The oscillator strengths of thiopyrylium, as estimated from the maximum extinction coefficient and half-widths are, however, too high by a factor of approximately 3 (68JPC3975). The same authors carried out PPP calculations on a series of pyrylium, thiopyrylium, and selenopyrylium derivatives comparing the results with experimental near UV and visible spectra. In most cases spectral features are well reproduced. The bathochromic shift observed along the series O-S-Se is explained by decrease of overlap between p -orbitals of the heteroatom and carbon (68TCA247). PPP calculations have also been used to evaluate alternative π -models for conjugated heterocycles, among which are pyrylium, thiopyrylium, and selenopyrylium (79MI2).

A detailed PPP–CI investigation of the unsubstituted pyrylium and thiopyrylium cations has been carried out by Japanese authors (72T5873). Electronic transition energies, oscillator strengths, π -orbital energies, π -electronic distributions, and π -bond orders were reported. From the amount of decrease of the positive charge on the heteroatom, the contribution of carbocationic resonance hybrid structures has been found to be 14.6% for thiopyrylium and 28.4% for pyrylium.

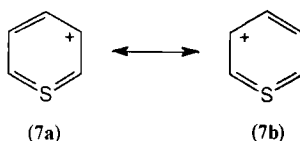
The PPP method has been extensively used for calculating the electronic absorption spectra of a number of substituted thiopyrylium ions. The substituents taken into account were mercapto (68TCA319), methyl (71T4705), phenyl (72CCC1520; 75MI1), *para*-aminophenyl (80JPR1), *para*-methylphenyl (72CCC1520), oxo (73JPR690; 87MI2), and thioxo (87MI2).

On the basis of PPP calculations, a mechanism for the sensitization of poly(vinylcinnamate) and poly(vinylcinnamylideneacetate) by 2,4,6-triphenylpyrylium and -thiopyrylium has been proposed (73CCC1668). With both polymers, the thiopyrylium salt is a more effective sensitizer than the corresponding pyrylium salt (72CCC1520).

Yoshida and co-workers have carried out a normal coordinate analysis for the in-plane and out-of-plane vibrations of thiopyrylium and pyrylium cations, in order to elucidate their infrared spectra (74T2099). The difference between the IR spectra of thiopyrylium and pyrylium has been attributed first to the mass effect of the heteroatom and second to the smaller contribution of the carbonium ion structures in the former ion than in the latter.

Semiempirical MNDO calculations have been carried out on model pyrylium and thiopyrylium systems (88MI1). The calculated HOMO-LUMO gap in the gas phase correlates well with experimental absorption maxima obtained in solution. Ionization potentials and electron affinities predicted by Koopmans' theorem with MNDO orbital energies do not track the observed trends in the experimental redox values. In contrast these are paralleled by the trends predicted by ΔH^0 values calculated by MNDO and AM1 for the open-shell and closed-shell species.

The question whether *d*-orbitals play an important role in the ground state bonding of thiopyrylium ion has aroused much controversy. Palmer and Findlay, using a nonempirical method involving linear combination of gaussian orbitals, concluded that sulfur 3*d* orbitals appear to behave as polarization functions rather than bonding orbitals in the normal chemical sense, and therefore, they are used only to a trivial extent (72TL4165). In contrast with this view, Yoshida and co-workers pointed out that the ¹H NMR spectra of thiopyrylium, pyrylium, and *N*-ethylpyridinium provide clear evidence of 3*d*-orbital participation in the former cation, as illustrated by resonance hybrids **7a** and **7b**. To support their view, they



carried out extended Hückel (EHMO) calculations using two basis sets, one with and another without sulfur 3*d* orbitals, and concluded that sulfur 3*d* orbitals are important to the bonding scheme of the thiopyrylium cation (73T2009). Palmer and co-workers replied that the electronic populations obtained by EHMO are physically unrealistic and explained the ¹H NMR observations on the basis of intramolecular electric fields and a greater ring current, due to its greater aromatic character, in the case of thiopyrylium ion [75JCS(P2)841]. Sándor and Radics calculated isotropic spin–spin coupling constants between spin-half nuclei for pyrylium, thiopyrylium, and selenopyrylium ions by the semiempirical SCPT–INDO method (85MI1). Apart from two-bond interactions, the theoretical values satisfactorily reproduced the signs, magnitudes, and the experimentally observed dependencies of the coupling parameters on the nature of the heteroatom. From comparison of the theoretical couplings calculated by means of *sp* and *spd* basis sets, it became evident that inclusion of *d* orbitals of sulfur or selenium atoms has only minor effects on theoretical coupling values. The coupling most affected is *J*(H2, H6), thus suggesting that the primary effect of *d* orbitals is polarization of the atomic orbital of α protons (Section II,C,2,a).

Charge distribution plays an important role in determining the reactivity of pyrylium and thiopyrylium cations, as shown in Fig. 1 (calculated from data given in Palmer *et al.* [75JCS(P2)841]). Because most of the positive charge is absorbed by protons, it seemed to be more appropriate to consider the total charge as partitioned among the heteroatom and the CH fragments. The reported values refer to an *sp* basis set in the case of pyrylium and to an *spd* + 3*s'* basis set in the case of thiopyrylium. In the latter case the values referring to an *sp* basis set are reported in parentheses. Comparing the results of the two basis sets in the case of thiopyrylium, it appears that the charge at the β position is practically unchanged, thus suggesting an insignificant contribution of resonance hybrids **7a** and **7b**. Moreover, it appears that inclusion of 3*d* orbitals yields a more even charge distribution. This has been recognized by other authors

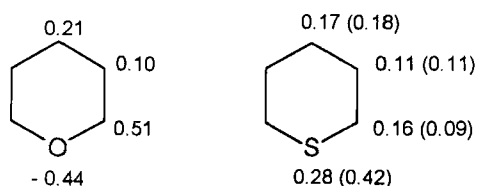


FIG. 1. Net charges at heteroatom and CH fragments of pyrylium and thiopyrylium ions (see text for further explanations).

as well (76KGS1627). Comparing the charge distribution in pyrylium and thiopyrylium ions, it appears that, in keeping with the higher electronegativity of oxygen vis-à-vis sulfur, the former cation has more carbonium ion character than the latter. Moreover, whereas in thiopyrylium α and γ positions have a similar charge density, in pyrylium the α position is significantly more densely charged than the γ one.

Various theoretical criteria have been suggested for establishing the aromatic character of the thiopyrylium ion. Yoshida and co-workers, on the basis of a normal coordinate analysis of vibrations and IR spectra, suggested that thiopyrylium is more aromatic than pyrylium (74T2099). Palmer and co-workers, taking into account the separation of the inner pair of π -electrons from the average of the quartet as evaluated by nonempirical calculations, gave the following order of aromaticity in the series of six-membered heteroaromatic rings of type 5 as a function of Z: CH > N > S⁺ > P > O⁺ > NH⁺ [75JCS(P2)841]. Using *ab initio* floating gaussian orbital calculations to evaluate the π -electron contribution to the molar susceptibility anisotropy and choosing benzene as the prototypical aromatic system, Blustin gave the following order of aromaticity as a function of Z: CH > S⁺ > N \approx P > SiH \approx O⁺ (79CPL347). Heats of formation derived from the AM1 semiempirical method were used by Dewar and Holder to determine the aromatic energies of a number of heteroaromatic systems. For six-membered heteroaromatic rings, they gave the following order of aromatic energies as a function of Z: CH > PH⁺ > S⁺ > P > N > SiH \approx O⁺ > NH⁺ (89HI135).

Other theoretical calculations that have been reported are MNDO studies of thiopyrylium (88MI2), 4-hydroxythiopyrylium, and 4-mercaptothiopyrylium [84ZN(A)267]; quantum chemical studies of thio- and selenopyrylocyanines having polymethine chains of variable length (73T2597, 73T2609; 81MI3; 86ZOR170; 88MI1, 88MI3; 91MI1, 91MI2); calculated hydride ion affinities for correlating observed hydrogen transfers and disproportionations of 2*H*- and 4*H*-thiopyrans (77KGS1206), and an *ab initio* calculation of ³³S nuclear quadrupole coupling constants of thiopyrylium using a triple zeta valence + polarization basis set [92ZN(A)203].

B. X-RAY STRUCTURES

The size of the chalcogens increases from a covalent radius of 0.73 Å for oxygen to 1.36 Å for tellurium. Thus the substitution of the larger chalcogens for oxygen in the pyrylium ring should alter the geometry of the ring. In particular the larger C—Z (Z = S, Se, Te) bond lengths relative to the C—O and C—C bond lengths should make the C2—Z—C6

bond angle markedly smaller than the nearly 120° C2—O—C6 bond angle found in pyrylium ions [82AHC(S)200-203]. The results of the few X-ray studies available on chalcogenopyrylium ions confirm the expectations.

The structure of the cocrystalline complex of bisphenol-A polycarbonate with 2,6-diphenyl-4-*p*-(dimethylamino)phenylthiopyrylium perchlorate shows that all four rings of the cation are planar but not coplanar (78MI1). The planes of the aryl substituents in the 2, 4, and 6 positions have dihedral angles of 37.7° , 12.4° , and 4.3° , respectively, with respect to the thiopyrylium plane. The nitrogen atom is coplanar with its three carbon neighbors and the plane of the dimethylamino group is nearly coplanar with the attached benzene ring (2.6° dihedral angle). This suggests that the quinoid resonance form must be important. Selected bond lengths and bond angles are reported in Fig. 2A.

The crystal structure of $[(2,4,6\text{-triphenylthiopyrylium})^+(\text{Cu}_2\text{I}_3)^-]$ has been determined at -120°C (82MI2). The cations are disordered over three orientations, so the accuracy of the heterocycle geometrical parameters is rather small. The heterocycle is approximately planar. The planes of the phenyl substituents in the 2, 4, and 6 positions form the dihedral angles 16.6° , 15.8° , and 15.9° , respectively, with the mean plane of the heterocycle. Selected bond lengths and bond angles are reported in Fig. 2B.

Symmetrical tetra-*tert*-butyl-substituted thiopyrylium monomethine perchlorate has been shown to be present in the *Z,Z* conformation both in solution (88KGS167) and in the solid state (90MI1; 91MI2). The X-ray structure shows that the two rings are nearly coplanar (1.2° dihedral angle)

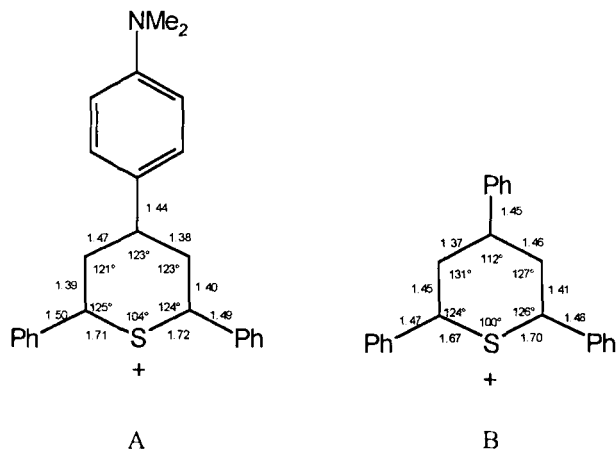


FIG. 2. Selected bond lengths (in Å) and bond angles (in degrees) for 2,6-diphenyl-4-*p*-(dimethylamino)phenylthiopyrylium ion (A) and 2,4,6-triphenylthiopyrylium ion (B).

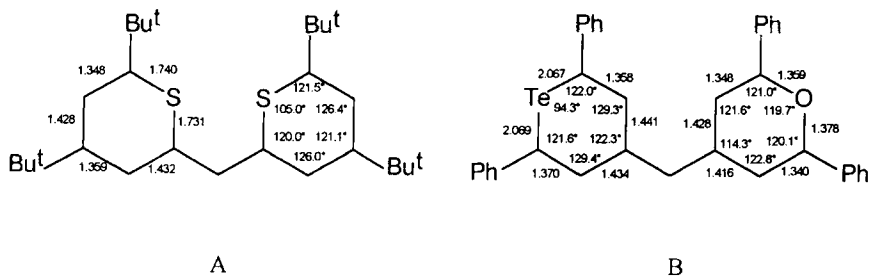


FIG. 3. Selected bond lengths (in Å) and bond angles (in degrees) for a thiopyrylium-thiopyrylium (A) and a telluropirylium-pyrylium (B) monomethine dye.

and have practically identical structural features. These are reported in Fig. 3A. Stabilization of the Z,Z conformation has been attributed to the presence of electronic interactions between the sulfur atoms. In contrast the corresponding pyrylo analog has been shown to be present in the Z,E conformation both in solution (88KGS167) and in the solid state (91MI2; 92M1ZSK139) (Section II,C,2,a). The mixed pyrylo-thiopyrylo derivative shows a Z,Z conformation in the solid state (91MI2; 92M1ZSK139).

No crystal structure is available for selenopyrylium cations.

The structure of a tetraphenyl-substituted telluropirylium-pyrylium monomethine fluoroborate shows that the telluropirylium ring is significantly distorted from the pyrylium ring (88M11). The pyrylium ring is bent 4.2° out of plane along the O-C γ axis, whereas the telluropirylium ring is bent 8.7° out of plane along the Te-C γ axis. Selected bond lengths and bond angles are reported in Fig. 3B. Noteworthy is the small C2—Te—C6 angle (94.3°).

C. SPECTROSCOPIC PROPERTIES

1. Optical Spectra

a. *Absorption Spectra.* Detailed UV spectra of unsubstituted pyrylium (1), thiopyrylium (2), and selenopyrylium (3) have been reported by Degani and co-workers (64G203). Data about the absorption maxima are reported in Table I. Yoshida and co-workers have shown that 2 in water, in contrast with 1, gives a third absorption maximum in the vacuum UV ($\lambda_{\max} = 195$ nm; ϵ not given) (72T5873). The reported UV spectra of chalcogenopyrylium ions lack vibrational structure.

TABLE I
UV SPECTRAL DATA OF PYRYLIUM,
THIOPYRYLIUM, AND SELENOPYRYLIUM,
PERCHLORATES IN ACETONITRILE^{a,b}

Compound	Band I	Band II
	λ_{\max} , nm (log ϵ)	λ_{\max} , nm (log ϵ)
1	270 (3.97)	219 (3.21)
2	284 (3.54)	245 (3.76)
3	300 (3.50)	267 (3.86)

^a Containing 1% of 70% aqueous HClO₄.

^b Degani *et al.* (64G203).

The absorption bands can be correlated to those of benzene (72T5873): the transition to the lowest energy level (band I in Table I) is the equivalent of the ${}^1B_{2u} \leftarrow {}^1A_{1g}$ transition of benzene at 256 nm (1L_b band in Platt notation), and the much greater intensity in chalcogenopyrylium ions must depend on the lower symmetry of these compounds (point group C_{2v}). This transition in chalcogenopyrylium ions is ${}^1B_1 \leftarrow {}^1A_1$; it is allowed in the molecular plane and perpendicular to the twofold rotation axis. Since the 1L_b band becomes less and less forbidden with increasing electronegativity of the heteroatom, the extinction coefficient increases in the order **3,2,1**. The 1L_b band is also shifted bathochromically in the same order. This has been interpreted in terms of the effectiveness of π -overlap between the heteroatom and the carbon π -framework (68TCA247). The transition to the second lowest energy levels (band II) is ${}^1A_1 \leftarrow {}^1A_1$; it is polarized along the twofold rotation axis and corresponds to the ${}^1B_{1u} \leftarrow {}^1A_{1g}$ (1L_a band in Platt notation) transition of benzene at about 200 nm. The 1L_a band also shows a bathochromic shift but, in contrast with the 1L_b band, appears to be shifted hyperchromically in going from **1** to **3**. The ${}^1E_{1u} \leftarrow {}^1A_{1g}$ transition of benzene at 180 nm is split to give ${}^1A_1 \leftarrow {}^1A_1$ and ${}^1B_1 \leftarrow {}^1A_1$ transitions in chalcogenopyrylium ions (1B_b and 1B_a in Platt notation). These cation transitions and the removal of degeneracy are permitted due to a decrease of the symmetry elements from D_{6h} to C_{2v} . PPP calculations have shown that the transition at 195 nm in **2** is due to the ${}^1B_1 \leftarrow {}^1A_1$ transition (72T5873). No low-energy $n \rightarrow \pi^*$ transitions have been evidenced in chalcogenopyrylium ions.

Early studies on the absorption of substituted thiopyrylium derivatives were carried out by Wizinger and co-workers (56HCA207, 56HCA217; 66HCA2046), who investigated the longest-wavelength absorption maxima of aryl thiopyrylium and thiopyrylocyanines, most of which had auxochromic groups in the *para* position.

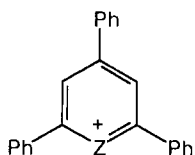
TABLE II
LONG-WAVELENGTH ABSORPTION MAXIMUM OF SOME SUBSTITUTED
CHALCOGENOPYRYLIUM IONS^a

Heteroatom	Substituents		Counter-ion	λ_{\max} , nm	log ϵ	Solvent	Ref.
	2,6	4					
O	H	<i>p</i> -NMe ₂ C ₆ H ₄	ClO ₄	500	4.73	CH ₃ CN	76JHC1089
				516	4.78	CH ₂ Cl ₂	76JHC1089
S	H	<i>p</i> -NMe ₂ C ₆ H ₄	ClO ₄	536	4.65	CH ₃ CN	76JHC1089
				558	4.77	CH ₂ Cl ₂	76JHC1089
Se	H	<i>p</i> -NMe ₂ C ₆ H ₄	PF ₆	591	4.95	CH ₂ Cl ₂	92MI2
Te	H	<i>p</i> -NMe ₂ C ₆ H ₄	PF ₆	628	4.90	CH ₂ Cl ₂	92MI2
O	Bu'	H	ClO ₄	293	3.95	CH ₃ OH	85UP1
S	Bu'	H	ClO ₄	310	3.98	CH ₃ OH	85UP1
Te	Bu'	H	PF ₆	345	3.92	CH ₂ Cl ₂	88MI4
O	C ₆ H ₅	H	ClO ₄	400	4.44	CH ₃ CN	83BSF(2)115
				416	4.12	CH ₂ Cl ₂	75MI1
				404	4.27	CH ₃ OH	85UP1
S	C ₆ H ₅	H	ClO ₄	419	4.11	CH ₂ Cl ₂	75MI1
				420	4.33	CH ₃ CN	73KGS857
				389	4.24	CH ₃ OH	85UP1
O	C ₆ H ₅	Me	ClO ₄	394	4.27	CH ₃ OH	85UP1
S	C ₆ H ₅	Me	ClO ₄	410	4.33	CH ₃ CN	73KGS857
O	C ₆ H ₅	OMe	ClO ₄	355	4.41	CH ₃ OH	81JA6148
S	C ₆ H ₅	OMe	ClO ₄	361	4.14	CH ₃ OH	85UP1
Te	C ₆ H ₅	OEt	FSO ₃	385	4.20	CH ₂ Cl ₂	82JOC5235
O	C ₆ H ₅	C ₆ H ₅	BF ₄	405	4.48	CH ₃ CN	80JA299
				417	4.43	CH ₂ Cl ₂	80JA299
				405 sh	4.34	CH ₃ CN	80JA299
S	C ₆ H ₅	C ₆ H ₅	BF ₄	420 sh	4.36	CH ₂ Cl ₂	80JA299
Se	C ₆ H ₅	C ₆ H ₅	ClO ₄	390	4.44	CH ₃ CN	73KGS857
O	C ₆ H ₅	<i>p</i> -NMe ₂ C ₆ H ₄	BF ₄	542	4.89	CH ₃ CN	88MI1
				550	4.91	CH ₂ Cl ₂	88MI1
				583	4.82	CH ₃ CN	88MI1
S	C ₆ H ₅	<i>p</i> -NMe ₂ C ₆ H ₄	BF ₄	592	4.83	CH ₂ Cl ₂	88MI1
				603	4.80	CH ₃ CN	88MI1
				620	4.81	CH ₂ Cl ₂	88MI1
Te	C ₆ H ₅	<i>p</i> -NMe ₂ C ₆ H ₄	BF ₄	636	4.76	CH ₃ CN	88MI1
				653	4.83	CH ₂ Cl ₂	88MI1

^a Substituents in positions 2 and 6 are identical. Positions 3 and 5 are unsubstituted.

In Table II are reported the spectral data of some series of chalcogenopyrylium ions possessing the same substitution pattern. It has been pointed out, in the case of pyrylium ions [82AHC(S)173-80], that on increasing the conjugative capacity of α and γ substituents, bathochromic and hyperchromic effects are observed. In particular, whereas α substituents mainly affect the 1L_b band, γ substituents practically only affect the 1L_a band. The latter effect is such that when the γ substituent has a conjugative capacity significantly greater than the α substituents, the 1L_a band appears at longer wavelength than the 1L_b band. The same behavior is shown by the chalcogen analogs of pyrylium.

From Table II it appears that the long-wave absorption maximum is increasingly shifted at longer wavelengths in the order O, S, Se, Te. 2,4,6-triphenyl-substituted cations **8**–**10** appear to be an exception, but the seemingly hypsochromic shift in going from O to Se is probably due to a simultaneous bathochromic shift of the 1L_a band and hypochromic shift of the 1L_b band. The latter appears as a shoulder of the 1L_a band in **9** and is probably submerged by the 1L_a band in **10**. Thus λ_{\max} refers to the 1L_b band for cations **8** and **9**, and to the 1L_a band for cation **10**.



(8) Z = O

(9) Z = S

(10) Z = Se

Solvent effects are evident on changing the dielectric constant of the solvent, as indicated in Table II for absorption maxima in CH_2Cl_2 and CH_3CN . The solvent with higher dielectric constant (CH_3CN , $\epsilon \sim 38$) gives a hypsochromic shift relative to the lower dielectric solvent (CH_2Cl_2 , $\epsilon \sim 9$). The solvent effect has been explained in terms of the higher dielectric constant solvent stabilizing the polar ground state more than the nonpolar first excited singlet state, resulting in a blue shift in absorption (80JA299; 88MI1).

Satisfactory linear relationships have been reported between the energy of the longest absorption maximum of a number of chalcogenopyrylium ions and the corresponding difference $E^0_{\text{ox}} - E^0_{\text{red}}$, thus suggesting that the HOMO–LUMO gap should be directly proportional to the energy of the absorption maximum (88MI1).

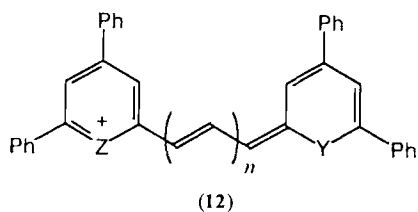
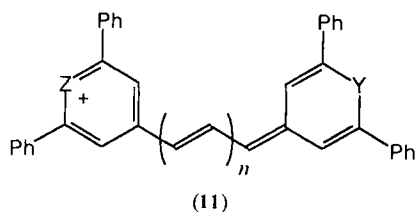
The values of λ_{\max} of some 2- and 4-(*p*-phenyl-substituted) pyrylium and thiopyrylium ions have been correlated with Hammett substituent

constants σ_p and σ_p^+ , in order to obtain, by interpolation, the substituent constants of the tetramethylguanidino group (92CJC2390).

Electronic spectra of 5,6-tri- and tetramethylenepyrylium and thiopyrylium salts have been investigated in different solvents (85KGS198).

Spectral properties of cyanine dyes incorporating chalcogenopyrylium nuclei at the ends of a polymethine chain, like **11** and **12**, have been investigated in great detail, especially by the group of Tolmachev and by Kodak's researchers; however, an account of the work done in this area is outside the scope of this review, and we limit ourselves to some general observations. Chalcogenopyrylium nuclei give large bathochromic shifts when incorporated in methine and polymethine dyes, much larger than other heterocyclic nuclei, resulting in absorption bands of high intensity in the visible and near-IR regions. Sequential bathochromic shifts are observed as the chalcogen atoms become heavier (74KGS53; 80UKZ1186; 82JOC5235; 84MI1; 88MI1). Each additional ethylene of separation between the two ends of the dye gives approximately a 100-nm bathochromic shift. The magnitude of this shift appears to be independent of the heteroatoms in the dye framework (82JOC5235). Perylo- and thiopyrylo-cyanines **12** (Z, Y = O, S; $n = 1, 2$) absorb at a longer wavelength and have a greater bandwidth than the corresponding γ, γ' isomers **11** (80KGS898; 84MI2); α, γ' isomers display an intermediate behavior (84MI2).

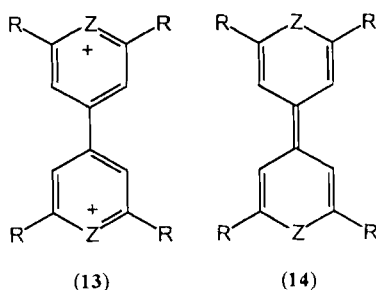
Hypsochromic shifts and band broadening have been observed for **11** (Z, Y = MeN, O, S, Se; $n = 0, 1, 2$) on changing the solvent from CH_2Cl_2 to CH_3NO_2 (80UKZ1186). A study of the dependence of UV-vis absorption-band widths, vinylene shifts, and oscillator strengths of **11** (Z = S, Y = Se; Z = O, Y = S, Se; Z = MeN, Y = O, S, Se; $n = 0-2$) on n has been made by quantum-chemical analysis of quadratic



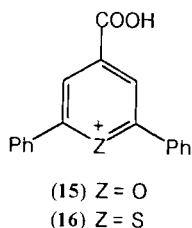
variations in bond orders on excitations (81MI3). Investigation of electron transitions in pyryloxyanines and their heteroanalogs has shown that the first transition is localized within the polymethine chain, and the higher ones are mainly localized within the end groups (91MI1). Vibronic interaction and shape of electron absorption bands have been also investigated (91UKZ1166).

Information on IR absorptions of chalcogenopyrylium ions is scarce. IR spectra of unsubstituted pyrylium (**1**) and thiopyrylium (**2**) have been reported by Yoshida *et al.* together with a normal coordinate analysis for the in-plane and out-of-plane vibrations (74T2099). Cation **2** yields lower absorption in wave number than **1** because of the mass effect of the heteroatom. The main reason for the difference in the IR spectra between benzene and heterocycles **1** and **2** is ascribed to the contribution of the carbonium ion structures in the latter cations. This contribution is larger in **1** than in **2** because of the electronegativity of the heteroatom (Section II,A).

Electronic and IR spectra of the bithiopyrylium **13** ($Z = S$, $R = Ph$), bithiopyranylidene **14** ($Z = S$, $R = Ph$), and polyiodide complexes of the latter have been analyzed as a function of charge-transfer degree and temperature (90MI2).

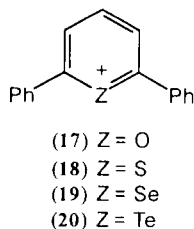


b. *Emission Spectra.* Although the fluorescence of arylthiopyrylium salts is evident both in solution and in the solid state (56HCA207), few studies have been dedicated to the subject. A detailed study of the emission properties of cations **15** and **16** has been carried out by Wintgens *et al.* [83BSF(2)115]. The authors reported for the two cations, the wavelength of the fluorescence maximum, the lifetime of the singlet excited state, and the fluorescence quantum yield at 20°C in CH_3CN . Moreover, they reported the wavelength of the phosphorescence maximum and the lifetime of the triplet state at $-196^\circ C$ in C_2H_5OH . The results indicate that the ~ 3 times lower fluorescence yield of **16** is due to a greater effectiveness of the forbidden transition singlet-triplet. Accordingly the phosphorescence intensity of **16** is ~ 50 times more important than that of **15**. Overall



the results suggest that the spin-orbit coupling is exalted by the presence of sulfur in **16**.

Wavelengths of the fluorescence maximum as well as fluorescence quantum yields in CH_2Cl_2 have been reported for the couples of cations **8**, **9** and **17**, **18** (75MI1). This study also indicates that thiopyrylium ions are less fluorescent, in terms of quantum yield, than pyrylium cations. Fluorescence and phosphorescence spectra of **9** have been discussed also in relation to the formation of charge-transfer complexes (74BCJ442).



Pyrylium and thiopyrylium salts show interesting emission properties when incorporated in a rigid polymeric matrix (85MI2). In addition to a strong rapid fluorescence emission, a delayed fluorescence is observed that cannot be detected in solution, even at -196°C .

Other studies that have been reported regard spectral and luminescent properties of some pyrylium and thiopyrylium salts (86MI1), emission properties of γ,γ' -chalcogenopyrylotrimethine cyanine dyes (90JA3845), and the effect of the polymethine chain length on the fluorescence spectra of symmetrical chalcogenopyrylocyanine dyes (92MI3).

c. *Charge-Transfer Spectra.* Few studies have been carried out on charge-transfer (CT) absorption bands involving thiopyrylium cations as electron acceptors, and none involving selenopyrylium and telluropyrylium cations.

2,4,6-Triphenylthiopyrylium tricyanomethanide (**9** · TCM) and 1,1,3,3-tetracyanopropen-3-ide (**9** · TCP) show a CT band in CHCl_3 centered at 566 and 595 nm, respectively (70BCJ3101). The CT band of the correspond-

ing pyrylium salts, **8** · TCM and **8** · TCP, is centered at 538 and 570 nm, thus indicating a smaller electron affinity of the pyrylium cations. The band is sensitive to the polarity of the solvent; an increase of the latter causes the absorption maximum to shift toward a shorter wavelength. This is expressed quantitatively by the linear correlation observed between Kosower *Z*-values and the energy of the CT band of **9** · TCP in various solvents. The CT band in the solid is at a shorter wavelength compared with that in solution.

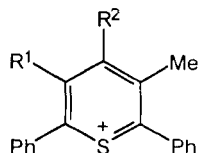
The effect of temperature on the CT band of **9** · TCP has been studied in a mixture 2-methyltetrahydrofuran-toluene 9 : 1 (74BCJ442). The CT absorption maximum shows a blue shift of 45 nm at -46°C and 120 nm at -196°C from the position of this band at room temperature. Such a shift has been explained as being due to the increase of solvent polarity at low temperature. A considerable decrease in absorbance of the CT band occurs together with the blue shift.

The emission spectrum of **9** · TCP has been studied revealing a CT fluorescence both in the solid state and in nonpolar rigid solution at -196°C , but not in fluid solution (74BCJ442). The CT complex **9** · TCP in the solid state shows exclusively a CT fluorescence, the emission from the component ions being completely quenched.

Cations **8** and **9** have been found to give CT complexes in CH_2Cl_2 also with a number of neutral donors, among which were diethylaniline, diphenylamine, triphenylamine, anthracene, and phenothiazine (77MI1). The energy of the CT band of the complexes of **9** reported against $E_{1/2}^{\text{ox}}$ of donors gives a roughly linear correlation as predicted by the theory. Analogous to the behavior of **9** · TCP, when the CT complex $[\text{Ph}_3\text{N} \cdot \text{9}]^+\text{ClO}_4^-$ is excited in the solid state only the CT emission is observed.

The unsubstituted thiopyrylium ion (**2**) has been found to form CT complexes in CH_3CN with both olefins and aromatic hydrocarbons (72CL17; 75BCJ1519). Two CT absorption bands have been observed in the former case, and one in the latter. The slope obtained by the plot of the CT transition energies vs the ionization potentials of donors is 0.27 for the olefin complexes and 1.04 for the aromatic hydrocarbon complexes. These slopes suggest that **2** interacts with olefins more strongly than with aromatic hydrocarbons. Strong interactions in the olefin complexes would manifest themselves also in the appearance of two CT bands. These have been ascribed to electronic transitions from the HOMO of the olefin donor to the lowest and the second lowest vacant orbital of **2**. The CT absorption frequencies of the complexes of **2** with olefins and aromatic hydrocarbons have been used to calculate their heat of formation by an empirical relation (81MI4).

Thiopyrylium cations **9**, **18**, **21**, and **22** form CT complexes with azide anion in acetonitrile (84T3539). The energy of the CT band of the complex formed by **21** and N_3^- in various solvents gave a good linear correlation with the Reichardt E_T solvent parameter.



(21) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$

(22) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$

2. Nuclear Magnetic Resonance Spectra

a. ^1H NMR Spectra. ^1H NMR data for the unsubstituted pyrylium (**1**), thiopyrylium (**2**), and selenopyrylium (**3**) cations in acetonitrile solution have been reported by Degani *et al.* (65MI2) and by Sándor and Radics (81OMR148). Chemical shifts and coupling constants obtained from iterative analyses using AA'BB'C approximation are summarized in Table III. The most remarkable fact about the chemical-shift data is the substantial decrease in the shielding of the α protons (H2, H6) on changing the heteroatom along the series O-S-Se. Since the trend is opposite what might be expected on the basis of calculated charge densities

TABLE III
 ^1H CHEMICAL SHIFTS^a (ppm) AND ^1H , ^1H
COUPLING CONSTANTS (Hz) OF PYRYLIUM,
THIOPYRYLIUM, AND SELENOPIRYLIUM
FLUOROBORATES IN CD_3CN ^b

	1	2	3
δ (H2)	9.58	10.08	10.98
δ (H3)	8.38	8.87	8.77
δ (H4)	9.20	9.05	9.03
3J (H2,H3)	4.21	8.73	8.95
4J (H2, H4)	1.84	1.06	1.12
5J (H2,H5)	1.00	0.89	0.95
4J (H2,H6)	0.40	3.45	3.08
3J (H3,H4)	8.11	8.47	8.80
4J (H3,H5)	1.46	0.82	0.53

^a Relative to TMS.

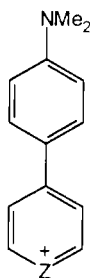
^b Sándor and Radics (81OMR148).

[75JCS(P2)841], the low proton shieldings in thio- and seleno-pyrylium ions have been rationalized by taking into account the magnetic susceptibility anisotropy effects of the heteroatoms. Dependent on the periodic number of the heteroatom and internuclear distances, anisotropy effects are expected to be more pronounced in the α positions and increase with heavier heteroatoms. At the β position, anisotropy effects have no sizable (if any) influence, as suggested by the fact that the H3, H5 chemical shift has its highest value in thiopyrylium. The chemical shift of the γ protons (H4) clearly reflects the partial charge at this position, which decreases in the order O, S, Se. Proton-proton couplings in the cations seem primarily affected by the electronegativity of the heteroatom (81OMR148).

By considering the chemical shift of the β protons of pyrylium and thiopyrylium, Yoneda *et al.* suggested that resonance structures **7a** and **7b** involving $(p-d)-\pi$ interactions contribute substantially to the ground state of thiopyrylium (73T2009). According to these structures, $(p-d)-\pi$ interactions increase electron deficiency of the β position and alter the π -bond orders of S—C2 and C2—C3 bonds. Theoretical calculations have shown that $3d$ -orbitals play the role of polarization functions rather than strongly bonding orbitals (Section II,A). However, the effect of $(p-d)-\pi$ interactions on some parameters is probably nonnegligible. Indeed comparison of experimental data for thiopyrylium and selenopyrylium is illuminating. Electronegativities of sulfur and selenium are very similar but interaction between p and d orbitals is more favorable for sulfur. In agreement with the expectations the chemical shift at the β position and the coupling through the heteroatom [$^4J(\text{H-2}, \text{H-6})$] exhibit higher values in thiopyrylium than in selenopyrylium (81OMR148). Moreover, SCPT-INDO calculations on pyrylium, thiopyrylium, and selenopyrylium, with sp and spd basis sets, show that the inclusion of d -orbitals gives a better agreement between the experimental and the calculated values of $^4J(\text{H-2}, \text{H-6})$ (85MI1).

The ^1H NMR spectrum of selenopyrylium in $\text{CF}_3\text{CO}_2\text{D}$ has been also reported (75OMR588); however, some of the pertinent transitions probably have been incorrectly assigned (81OMR148).

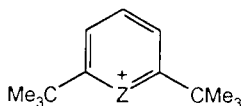
The less substituted telluopyrylium cation, whose ^1H NMR spectrum is available, is the 4-(p -dimethylaminophenyl) derivative **24**; ^1H NMR data in CD_2Cl_2 for the heteroaromatic ring protons of **24** are $\delta(\text{H2}) = 10.60$, $\delta(\text{H3}) = 8.80$, $^3J(\text{H2}, \text{H3}) = 11.6$ Hz (92MI2). It is interesting to compare these data with those for the seleno analog **23**: $\delta(\text{H2}) = 9.48$, $\delta(\text{H3}) = 8.61$, $^3J(\text{H2}, \text{H3}) = 10.6$ Hz (92MI2). Apart from the increase of $\delta(\text{H3})$ in going from **23** to **24**, the trends of $\delta(\text{H2})$ and $^3J(\text{H2}, \text{H3})$ are those expected on the basis of the data reported in Table III.



(23) Z = Se

(24) Z = Te

NMR data for the series of 2,6-di-*tert*-butyl chalcogenopyrylium ions **25–28** are summarized in Table IV. Noteworthy is the increase of $^3J(\text{H-3}, \text{H-4})$ on changing the heteroatom from selenium to tellurium.



(25) Z = O

(26) Z = S

(27) Z = Se

(28) Z = Te

The chemical shift of the methyl group in methyl-substituted pyrylium, thiopyrylium, and selenopyrylium cations is reported in Table V. Whereas for pyrylium and thiopyrylium the order of chemical shift of methyl group is: $\alpha > \gamma > \beta$, in the case of selenopyrylium the order is $\alpha > \beta > \gamma$. The presence of additional methyl groups causes only small

TABLE IV
 ^1H CHEMICAL SHIFTS^a (ppm) AND ^1H , ^1H COUPLING
CONSTANTS (Hz) OF 2,6-DI-*tert*-BUTYL
CHALCOGENOPYRYLIUM HEXAFLUOROPHOSPHATES^b

	25 ^c	26 ^c	27 ^c	28 ^d
δ (H3)	8.10	8.69	8.55	8.50
δ (H4)	9.09	8.94	8.93	8.97
δ (<i>t</i> -Bu)	1.58	1.65	1.69	1.68
3J (H3, H4)	8.2	8.5	8.8	9.6

^a Relative to TMS.^b Detty (88MI4).^c Solvent: CD_2Cl_2 .^d Solvent: CDCl_3 .

TABLE V
¹H CHEMICAL SHIFTS^a (ppm) OF THE
 METHYL GROUP IN 2-,3-, AND 4-METHYL
 PYRYLIUM (O), THIOPYRYLIUM (S), AND
 SELENOPYRYLIUM (Se) PERCHLORATES^b

	O	S	Se
δ (Me2)	2.92	3.17	3.19
δ (Me3)	2.46	2.83	2.82
δ (Me4)	2.75	2.92	2.75

^a Relative to TMS.

^b Solvent: CH₃CN containing 1% of 70% aqueous HClO₄. Values taken from Degani *et al.* (67MI2).

chemical-shift variations with respect to the values reported in Table V (74UKZ287). The chemical shift of the γ -methyl group in 2,6-di-*tert*-butyl-4-methyltelluropyrylium fluoroborate is 2.53 ppm in CDCl₃ (86MI2) and 2.56 ppm in CD₃CN (88MI1), i.e., ca. 0.2 ppm at higher magnetic field than the γ -methyl group in selenopyrylium ions. No other information is available about methyl groups in telluropyrylium derivatives.

In phenyl-substituted pyrylium ions, *ortho* protons of α - and γ -phenyl groups resonate at lower fields than *meta* and *para* protons; in thiopyrylium derivatives the separation between the *ortho* signals and the *meta* and *para* ones is lower and not always appreciable; in selenopyrylium derivatives it is decidedly not significant (74UKZ287).

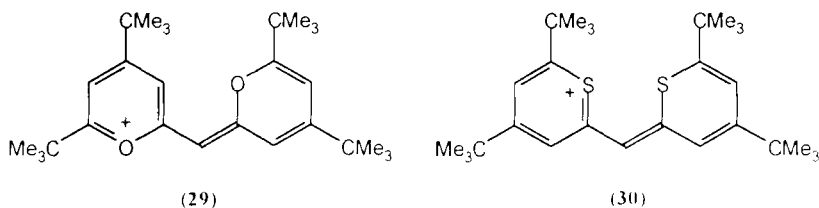
¹H NMR data have been reported for 2,6-dimethyl- and 2,6-diphenyl-4*H*-pyran-4-one and -thiopyran-4-one and -selenopyran-4-one, in their neutral and protonated forms (75MI2).

A certain number of chemical problems has been faced and resolved by ¹H NMR spectroscopy. The kinetics of deuterium exchange in the methyl groups of some pyrylium, thiopyrylium, and pyridinium salts has been studied in methanol. The activating effect of the heteroatoms changed in the sequence O > S > N. In the pyrylium and thiopyrylium salts, the mobility of the protons of the γ -Me group was greater than that of the α -Me group (69MI2).

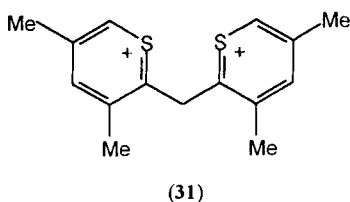
The addition of methoxide ion to pyrylium and thiopyrylium cations has been studied in various solvents (80JOC5160). Kinetic and thermodynamic regioselectivities for the methoxide addition have been obtained in methanol at -40 and 25°C, respectively [86JCS(P2)271].

^1H and ^{13}C NMR spectra indicate that 2,6-dimethyl-4*H*-pyran-4-one and -thiopyran-4-one in $\text{HSO}_3\text{F}\text{-SbF}_5$ solution are doubly protonated at the exocyclic oxygen atom [81JCS(P2)812].

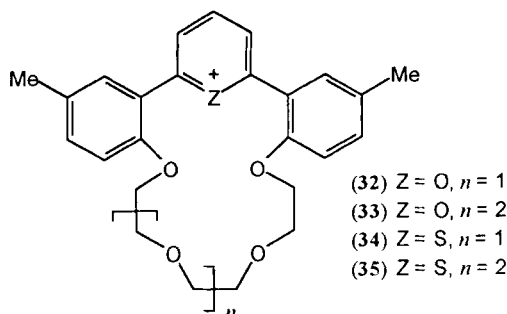
Symmetrical tetra-*tert*-butyl-substituted pyrylium and thiopyrylium monomethine dyes have been shown by ^1H NMR to be mainly present in solution in the conformation E,Z (**29**) and Z,Z (**30**), respectively (88KGS167) (Section II,B). Conformational analysis of monomethine and trimethine cyanine dyes containing pyrylium and thiopyrylium nuclei has been also carried out using nuclear Overhauser effect (89MI1).



Dication **31**, formed by protonation of the corresponding thiopyrylium monomethine dye at the methine carbon, has been shown by ^1H NMR to be present in solution in two conformations, each giving distinct resonance signals [80BSF(2)434].



^1H NMR spectra of $\text{CF}_3\text{CO}_2\text{H}$ solutions of cyanine dyes **11** ($Z = Y = \text{O}, \text{S}, n = 0\text{--}3$) and model compounds have shown that protonation occurs at the CH adjacent to the heterocyclic ring (76MI2).



An interesting effect has been observed in the ^1H NMR of corands **32–35** incorporating pyrylium and thiopyrylium subunits. By increasing the length of the poly(oxyethylene) bridge, the β -protons are deshielded by ca. 0.2 ppm and the γ -protons are slightly shifted upfield, thus causing, in the case of the thiopyrylium derivatives, a change of the spin system from AB_2 to A_2B . Comparison with acyclic model compounds showed that this effect is due to a reduced proximity between *ortho*-oxygen and β -protons because of the hindrance of the poly(oxyethylene) bridge, in particular of the shorter one (91T1977).

b. ^{13}C NMR Spectra. ^{13}C NMR data for pyrylium (**1**), thiopyrylium (**2**), and selenopyrylium (**3**) as obtained by iterative calculations by means of the $\text{AA}'\text{BB}'\text{CX}$ ($\text{X} = ^{13}\text{C}$) approximation, are reported in Table VI (81OMR148). On changing the heteroatom, the shielding of the ^{13}C nuclei at the β and γ positions shows the same trend noted for protons. In

TABLE VI
 ^{13}C CHEMICAL SHIFTS^a (ppm), ^{13}C , ^1H COUPLING
CONSTANTS (Hz), ONE- AND THREE-BOND ^{13}C ,
 ^{13}C COUPLING CONSTANTS (Hz) OF PYRYLIUM,
THIOPYRYLIUM, AND SELENYOPYRYLIUM
FLUOROBORATES IN CD_3CN ^b

	1	2	3
δ (C2)	169.33	158.78	170.73
δ (C3)	127.74	138.27	137.30
δ (C4)	161.20	150.81	149.47
1J (C2,H2)	216.28	190.10	191.24
2J (C2,H3)	7.90	4.77	4.82
3J (C2,H4)	6.80	8.11	8.92
4J (C2,H5)	-0.94	-0.87	-1.10
3J (C2,H6)	6.31	5.95	4.58
2J (C3,H2)	9.32	-0.23	0.11
1J (C3,H3)	181.57	176.37	173.09
2J (C3,H4)	1.02	1.23	0.92
3J (C3,H5)	6.52	6.80	6.88
4J (C3,H6)	-1.05	-0.97	-1.01
3J (C4,H2)	4.94	6.53	7.20
2J (C4,H3)	-0.24	0.71	0.74
1J (C4,H4)	177.66	172.26	170.35
1J (C2,C3)	59.5	56.5	56.7
1J (C3,C4)	50.4	54.3	55.4
3J (C2,C5)	9.4	9.8	9.3

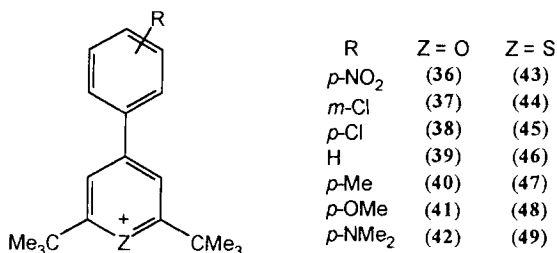
^a Relative to TMS.

^b Sándor and Radics (81OMR148).

contrast to the proton shifts, the relatively high shielding of the α carbons in thiopyrylium may be due to a drastic drop in the "effective nuclear charge" with respect to that in pyrylium, an effect that cannot be offset by the magnetic anisotropy of the sulfur atom. The $^1J(\text{CH})$ coupling constants are substantially larger than in the corresponding five-membered neutral chalcogens. Their values decrease with the increasing number of bonds separating the heteroatom and the C—H pair considered, i.e., $^1J(\text{C2,H2}) > ^1J(\text{C3,H3}) > ^1J(\text{C4,H4})$. Moreover, with the exception of $^1J(\text{C2,H2})$ in the pair thiopyrylium–selenopyrylium, they vary with the electronegativity of the heteroatom. Although the long-range C,H couplings appear to be affected mainly by the electronegativity of the heteroatom, there are deviations that might be indicative of effects due to π -electrons (81OMR148). SCPT–INDO calculations have shown that the mutual polarizability of interacting nuclei represents a good qualitative measure of the main factors that influence the magnitude of $^1J(\text{C,H})$ and $^1J(\text{C,C})$ (85MI1).

The ^{13}C chemical shifts of 2,6-di-*tert*-butyl-4-arylpyrylium and thiopyrylium ions **36–49** have been determined in CD_3CN (88G291). Since the substituent-induced chemical shift (SCS) of the *para* carbon in monosubstituted benzenes reflects the overall electronic effect of the substituent, those of cations **39** and **46** (6.84 and 4.60 ppm, respectively, relative to benzene in CD_3CN) reveal that pyrylium and thiopyrylium moieties behave as good electron-withdrawing substituents, comparable to NO_2 [SCS = 6.18 ppm (80JOC2429)] and COMe [SCS = 4.67 ppm (80JOC2429)] groups, respectively. Whereas the C4 chemical shifts of the two heteroaromatic rings are largely affected by π -polarization, as shown by the shielding induced by electron-withdrawing substituents, the C2 and C3 chemical shifts are free from such effect. The effects of nonadditivity of chemical shifts, when pyrylium or thiopyrylium are the fixed groups in *para*-disubstituted benzenes, have been analyzed (88G291) according to the single-parameter equation proposed by Lynch (77CJC541).

^{13}C chemical shifts of α , β , and γ carbon atoms of some phenyl-substituted thiopyrylium salts (84T3549) and ^{13}C shift effects for the series



formed by thiopyran-2-thione, 2-ethylthio-thiopyrylium, and unsubstituted thiopyrylium (87PS187) have been reported.

c. ^{77}Se and ^{125}Te NMR Spectra. ^{77}Se NMR data for selenopyrylium (**3**) are reported in Table VII. The chemical shift of the ^{77}Se nucleus is approximately 370 ppm higher than the value reported for the electrically neutral selenophene (74OMR648). The most prominent features of the coupling patterns in Table VII are that the signs of the $^nJ(\text{SeC})$ are opposite of $^{n+1}J(\text{SeH})$. These coupling patterns are, in terms of the signs of the reduced coupling constants, identical with those reported for $^nJ(^{15}\text{NC})$ and $^{n+1}J(^{15}\text{NH})$, respectively, in pyridine (76TL1621).

^{125}Te chemical shifts of telluropyrans, telluropyranones, and telluropyrylium salts in both the Te(II) and Te(IV) oxidation states have been reported (89MI2). 2,6-Di-*tert*-butyltelluropyrylium ion (**28**) had the furthest downfield chemical shift (δ 1304 ppm relative to Me_2Te). Introduction of a methyl substituent at the 4-position resulted in a more electron-rich tellurium center as evidenced by an upfield shift to δ 1185 ppm. In telluropyrylium dye chromophores having *p*-anisyl and/or *p*-*N,N*-dimethylaminophenyl substituents, the ^{125}Te chemical shifts were even further upfield in the range δ 784–934 ppm. The effect of the positive charge is dramatic: the ^{125}Te chemical shift of 2,6-di-*tert*-butyl-4*H*-telluropyran was 257 ppm, i.e., more than 1000 ppm upfield of the corresponding telluropyrylium salt. A linear correlation was found for seven telluropyrylium salts between the ^{125}Te chemical shifts and the $\text{Te}(3d_{5/2})$ binding energies obtained by XPS.

3. Electron Spin Resonance Spectra

2,4,6-Triphenylthiopyrylium (**9**) is reduced by zinc powder in cyclohexane to yield the stable radical **51** (67MI3), whose ESR spectrum has been completely resolved and analyzed (70MP613). The assignment of the hyperfine coupling constants was accomplished by investigating the

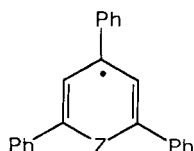
TABLE VII
 ^{77}Se CHEMICAL SHIFT^a (ppm), $J(\text{Se,H})$ AND $J(\text{Se,C})$ VALUES (Hz) OF
SELENOPYRYLIUM FLUOROBORATE IN CD_3CN ^b

$\delta(^{77}\text{Se})$	$^2J(\text{Se,H2})$	$^3J(\text{Se,H3})$	$^4J(\text{Se,H4})$	$^1J(\text{Se,C2})$	$^2J(\text{Se,C3})$	$^3J(\text{Se,C4})$
975.7	45.25	6.16	−2.36	−155.4	−13.3	22.9

^a Relative to Me_2Se .

^b Sándor and Radics (81OMR148).

spectra of deutero and ^{33}S -enriched derivatives, and by simulation of the spectrum. The Lande g factor (2.0041) was not affected by deuteration and the difference with the g value of the pyrylium analog **50** (2.0031) is consistent with a greater spin-orbit interaction of the unpaired electron on the sulfur atom. The hyperfine coupling constants of the heterocyclic protons of **51** are larger than the corresponding couplings in the pyranil radical **50** (68MP217). The opposite is found for the phenyl protons, the largest difference being observed for the 4-phenyl group. These features indicate a lower delocalization of the unpaired electron on the phenyl rings in the thiopyranil radical, in agreement with the greater ability of the sulfur atom in radical stabilization. The spin density distribution was calculated by the McLachlan method. The best fit between the experimental coupling constants and those calculated by McConnell equation was found when the α phenyl groups are twisted 42° and the γ phenyl group is twisted 31° from the heterocyclic plane.



(50) $Z = \text{O}$

(51) $Z = \text{S}$

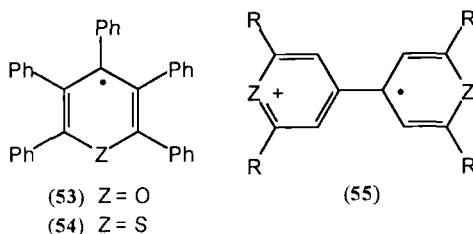
(52) $Z = \text{Se}$

Niizuma *et al.* reported the ESR spectra, at room and low temperature, of radicals **50** and **51** obtained by photochemical reduction in tetrahydrofuran and/or 1,2-dimethoxyethane of corresponding cations **8** and **9** (85BCJ2600). The coupling constants determined by simulation of the ESR spectra coincided within the experimental errors with those obtained by ENDOR. Comparison of the coupling constants with those obtained by Degani *et al.* (68MP217; 70MP613) shows good agreement in the case of **50** but not in the case of **51**.

Radicals **50** and **51** were also evidenced by ESR as the products of an electron-transfer reaction of cations **8** and **9**, respectively, with either $\text{Pr}'\text{O}^-$ or $\text{Bu}'\text{O}^-$ in the corresponding alcohols (86ZC400).

Wintgens *et al.* studied the dimerization equilibria of radicals **50** and **51**, respectively, by integrating the area of the ESR signals at various temperatures (86NJC345). Although it is commonly accepted that the dimers are due to γ, γ' coupling of the radicals, there are electrochemical evidences which suggest, for **50**, that also α, α' and α, γ' dimers are involved in the equilibrium (80MI2). At room temperature the radical is the favored

species, whereas a decrease of temperature displaces the equilibrium in favor of the dimeric compound. The equilibrium constants and the standard enthalpy variations for the dimerization of **50** ($K_D 3 \times 10^4$ liters mol⁻¹ at -10°C, $\Delta H^\circ_D -16.0$ kcal mol⁻¹) and **51** ($K_D 2 \times 10^3$ liters mol⁻¹ at -10°C, $\Delta H^\circ_D -10.7$ kcal mol⁻¹) indicate a higher stability of the sulfur containing radical (86NJC345). A similar study concerning the dimerization of radicals **53** and **54** was carried out by Kawata and Niizuma (89BCJ2279). Owing to steric hindrance of the phenyl groups in the dimers, the dimerization equilibria were found to be endothermic.



One-electron reduction of 4,4'-bithiopyrylium dication [**13** (Z = S, R = H)] with zinc in CH₃CN, at room temperature, yields the corresponding radical cation **55** (Z = S, R = H), whose hyperfine ESR spectrum consists of five overlapping pentuplets, resulting from coupling with four equivalent H_β protons (0.60 G) and four equivalent H_α protons (2.37 G). The spectrum pattern indicates that the odd electron is distributed equally in both rings (72CC60).

Radical cations **55** (Z = O, S, Se, Te, R = Bu') generated in a coulometric flow reactor in CH₂Cl₂ have been examined by ESR (85T4853). Whereas the spectra for Z = O and Z = S have five lines, those for Z = Se and Z = Te have featureless and broad single lines. Linewidths and *g* values increase in the sequence O, S, Se, Te. This order is related to the spin-orbit coupling, which increases with increasing atomic number. A plot of *g* values vs the spin-orbit coupling constants shows a good linear relationship, thus indicating that the spin populations on the heteroatoms in **55** are approximately constant. The low value of the slope indicates that the unpaired spin is localized mainly in the carbon π framework.

The microcrystalline CT salts between cations **8** and **9** and the anions 1,1,3,3-tetracyanopropenide and tricyanomethanide showed a single broad ESR absorption band. The CT salts showed a photocurrent about 10 times larger than the dark current on irradiation at the CT absorption band. The ESR signal, which seems to originate from the charge carriers in the dark conduction, was slightly enhanced on the CT and near IR excitations (74BCJ448).

The ESR spectra of different polyiodide complexes of bithiopyranylidene **14** ($Z = S$, $R = Ph$) in the solid state have been reported as broad single lines (81MI5).

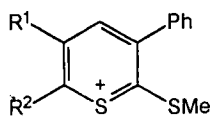
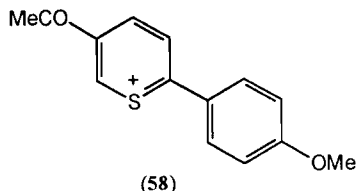
Zinc reduction of thiopyrylocyanine **11** ($Z = Y = S$; $n = 0$) affords the corresponding radical, which, studied by ESR, shows significant electron delocalization in the two thiopyrylium fragments. The same thiopyrylocyanine has been also oxidized with PbO_2 to give the corresponding dication radical, which undergoes the loss of the methinic proton to yield a cation radical. The latter has been evidenced by ESR (90KGS1480). The ESR spectrum of the one-electron zinc reduction product of 9-phenyl-1,2,3,4,5,6,7,8-octahydrothioxanthylum cation has been also reported (91KGS47).

4. Mass Spectra

The electron-impact mass spectra of bromides, iodides, and fluoroborates of the 2,4,6-triphenyl-substituted cations **8** and **9** have the base peak at the mass number of the cation (74OMS80). No molecular ion peak of an adduct between the cation and the anion has been found; the fluoroborates show also weak peaks with the elemental composition of an adduct between the cation and F^- . On the contrary, the spectra of perchlorates do not show the peaks at the mass number of the cation but peaks indicating the addition of an oxygen atom and the removal of a hydrogen atom. From ionization potential measurements it has been shown that the bromides, iodides, and fluoroborates of **8** and **9** are thermally reduced in the mass spectrometer to volatile free radicals **50** and **51** prior to evaporation, presumably with concomitant oxidation of the anion. In the presence of a nonoxidizable anion, e.g., perchlorate, reduction of the cations to free radicals does not take place. Interestingly, the order of ionization potentials of the radicals, **50** < **51**, indicates that the LUMO energy level of pyrylium is higher than that of thiopyrylium, consistent with electrochemical studies (Section II,D).

The mass spectra of 2,6-dimethylthio-3-phenylthiopyrylium (**56**) perchlorate and iodide, and 5-formyl-2-methylthio-3-phenylthiopyrylium (**57**) perchlorate have been discussed in detail (76BSF1195). With perchlorate as counter-ion, fragments corresponding to oxidation products of thiopyrylium have been found.

In the mass spectrum of 5-acetyl-2-(*p*-methoxyphenyl)thiopyrylium (**58**) perchlorate, the most abundant ion is that resulting from the capture of a hydrogen atom, followed by loss of the acetyl group. Relative abundance of the peaks $[M]^+$ and $[M + 1]^+$ is 10 and 28%, respectively (75T3059).

(56) $R^1 = \text{H}$, $R^2 = \text{SMe}$ (57) $R^1 = \text{CHO}$, $R^2 = \text{H}$ 

(58)

Mass spectrometry has been used to characterize 4,4'-bithiopyrylium iodide and fluoroborate. Besides the strong molecular peak, intense fragments are observed for the loss of one and two sulfur atoms (71TL3999).

Fast atom bombardment mass spectrometry appears to be a useful tool in the analysis of pyrylium, thiopyrylium, and pyridinium salts [87JCS(P2)633]. All the examined salts gave large peaks corresponding to the intact cations. Fragmentation is totally absent when only phenyl substituents are present on the heterocyclic rings, whereas alkyl substituents are responsible for alkane, alkene, or alkyl losses. Unusual fragmentation patterns have been observed in the spectra of halogeno-derivatives, such as **38**, **44**, **45**, and nitro-derivatives, such as **36** and **43**. In the former case peaks arising from a dehalogenation process with addition of H are observed, whereas in the latter case the peaks have been ascribed to partial and complete reduction of the nitro group to hydroxylamine and amine, respectively. Both processes are probably due to bombardment-promoted reactions of the cations with the matrix.

The formation of thiopyrylium (**2**) as a rearrangement ion has been invoked in the electron impact mass spectra of 2- and 3-alkylthiophenes (59CCC1602; 88IZV905). The tendency toward the formation of **2**, which represents the most abundant species, grows as the side-chain increases in length. Cation **2** has been also detected in the reaction zone of a $\text{C}_6\text{H}_6/\text{CS}_2/\text{H}_2$ flame, by flame ionization/mass spectroscopy (84AJC511).

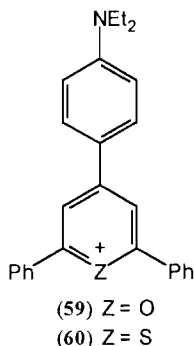
Fragmentations to thiopyrylium ions constitute a typical model for various 2*H*-thiopyrans (75T53, 75T3059; 76OMS293, 76OMS364; 86JPR567).

5. X-Ray Photoelectron Spectra

High-resolution XPS spectra have been reported for bithiopyranylidene **14** ($Z = \text{S}$, $R = \text{Ph}$), three of its polyiodides, and bithiopyrylium perchlorate **13** ($Z = \text{S}$, $R = \text{Ph}$) (82MI3). From the $\text{S}(2p_{3/2})$ binding energy of **13** it has been determined that the charge on each sulfur atom is +0.26, thus the carbon framework has to carry a charge of +1.48 in a purely ionic picture. Accordingly a shoulder appears on the left side of the $\text{C}(1s)$ line of **13**. The strongest peak contains the $\text{C}(1s)$ levels of the phenyl carbon atoms, whereas the shoulder has been attributed to the dithiopyranyl

carbon atoms. The peak at 1.2 eV of **14** identified as the HOMO completely disappears in the dication valence band.

Solid-state XPS spectra of cations **59** and **60** have been reported (82MI4). Clearly resolved, intense shake-up excitations ($\sim 20\%$ of the main peak intensity) are associated with N(1s) ionization, whereas heteroatomic ionization in the chalcogenopyranyl moiety yields shake-up intensities of 20–30%. Heteroatomic binding-energy differences (ΔBE) in accordance with experiment are extracted from charge-potential calculations. It is concluded that ΔBE are a sensitive function of the ion/counter-ion pairing scheme.



Detty *et al.* reported a XPS analysis of several series of telluropyranyl, telluropyranone, and telluropyrilium compounds in both the Te(II) and the Te(IV) oxidation states (89MI2). Two linear correlations were found between ^{125}Te NMR shifts and Te($3d_{5/2}$) binding energies for the neutral and cationic Te(II) compounds, respectively, whereas the Te(IV) compounds showed no apparent correlation (Section II,C,2,c).

D. ELECTROCHEMICAL PROPERTIES

Chalcogenopyrylium cations can be reduced and oxidized electrochemically. The two processes can be either reversible or irreversible, depending on the substituents present on the heterocyclic ring.

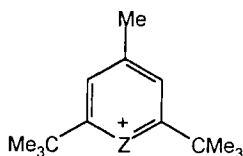
2,4,6-Triphenyl substituted cations **8–10** undergo reversible electrochemical reduction to yield the corresponding radicals **50–52** (80JA299, 80UKZ1186; 86NJC345; 86ZOB863). The reduction potential is increasingly negative in the order Se, S, O. This trend, which is due to a decreased stabilization of cation LUMO (80JA299), has been interpreted in terms of either the different electron affinities of the heteroatoms (Se > S > O)

(86ZOB863) or the increased π -overlap of the heteroatom in going from Se to O (see below).

Chalcogenopyranyl radicals tend to dimerize. Equilibrium dimerizations have been studied by voltammetric methods (80MI2), ESR, and UV-vis methods (86NJC345) (Section II,C,3). Pragst *et al.* have shown that coupling of the radical **50** can involve both the α and the γ positions, γ,γ' dimer being the kinetically favored isomer and α,α' dimer being the thermodynamically more stable one (80MI2). When the γ position is unsubstituted, like in **17**, **18**, **19**, the reduction potentials become less negative and the radicals dimerize irreversibly to yield the corresponding γ,γ' dimers (80MI2; 86ZOB863).

The reduction of cations **25–28**, as determined by cyclic voltammetry, has been found to be irreversible. The cathodic peak potential is increasingly negative in the order Te, Se, S, O (88MI4). The positive scan following reduction shows an irreversible oxidation that can be ascribed to oxidation of the γ,γ' dimers formed after reduction of the cations. The anodic peak potential does not show a definite trend on changing the heteroatom. The behavior of cation **28** has been investigated in greater detail, showing that the oxidation of the corresponding γ,γ' dimer requires 2.6 F/mol and regenerates 2 equiv of **28**. Analogous behavior had been shown by the γ,γ' dimer obtained after reduction of **17** (77JPR952).

Also, the cations **61–64** having a methyl group in γ position are reduced irreversibly because of formation of a γ,γ' dimer (88MI1).



(61) Z = O

(62) Z = S

(63) Z = Se

(64) Z = Te

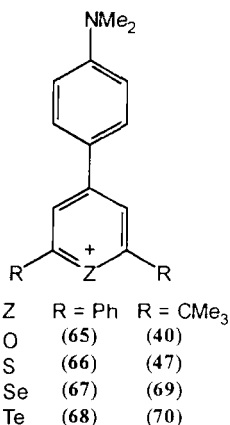
The LUMO energy level of chalcogenopyrylium ions is decreased by electron-withdrawing substituents and increased by electron-releasing substituents. For example, cations **15** and **16** are reversibly reduced at potentials less negative than cations **8** and **9** (86NJC345), whereas cations **59** and **60** are reduced at more negative potentials (80JA299). A decrease of the LUMO energy level of the cation increases the stability of the corresponding radical, which is thus less prone to dimerize (86NJC345).

Chalcogenopyrylium ions that are reduced reversibly to the corresponding radicals may be further reduced to yield the corresponding antiaromatic

anions. Representative cations that have shown this behavior are **8**, **9**, **59**, **60** (80JA299), **11** ($Z = \text{Te}$, $Y = \text{O}$, S , Se , Te , $n = 0$), and **65–68** (88MI1). The redox data suggest that π -donation from the heteroatom to the carbon π -framework is important in determining the stability of the various states. According to the π -donating ability of chalcogens ($\text{O} > \text{S} > \text{Se} > \text{Te}$), oxidation of the radical to the aromatic cation is increasingly positive in the order O , S , Se , Te , whereas reduction of the radical to the antiaromatic anion is increasingly negative in the order Te , Se , S , O ; in other words, the increased π -overlap stabilizes the cation and destabilizes the anion (88MI1).

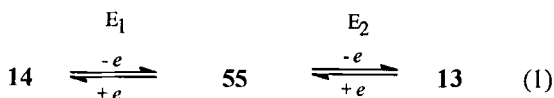
The anions obtained by two-electron cathodic reduction of cations **8** and **9** undergo alkylation in the presence of an alkyl halide (80MI3; 90ACS524). It has been suggested that the reaction between 2,4,6-triphenylthiopyranyl anion and *tert*-butyl bromide takes place via a rate-determining electron transfer from the anion to the alkyl halide, followed by combinations of the radicals (90ACS524).

Pragst and Rudenko have studied the anodic behavior of **8** and **9** in 0.1 *M* $\text{CH}_3\text{CO}_2\text{H}/\text{HSO}_3\text{F}$ at -76°C (83JPR627). The cations have been oxidized to the corresponding dication radicals. Voltammograms display typical marks of the anodic aromatic dimerization, which seems to involve the phenyl groups. The presence of an electron-releasing group, like in **59** and **60**, makes the oxidation potential experimentally accessible also in CH_3CN (80JA299). Other representative cations that have been reversibly oxidized in CH_3CN are **65–68**, **42**, **49**, **69**, **70** (88MI1). The oxidation potential of chalcogenopyrylium ions is increasingly positive in the order Te , Se , S , O . It appears therefore, that the easiest chalcogenopyrylium ion to oxidize is also the easiest to reduce. This implies a narrowing of



the HOMO–LUMO gap as the heteroatom becomes heavier. This trend is in accordance with the sequential bathochromic shifts observed in the absorption spectra, as illustrated by the satisfactory linear correlations that have been found between the energy of the absorption maxima and the HOMO–LUMO gaps determined by redox potentials (88MI1) (Section II,C,1,a).

Hünig and co-workers have investigated the polarography of 4,4'-bipyrylium, bithiopyrylium, and bipyridinium salts in CH_3CN (73LA1036). The process involves two reversible one-electron processes, involving the dication **13**, the radical cation **55**, and the neutral compound **14**, as indicated by Eq. (1).



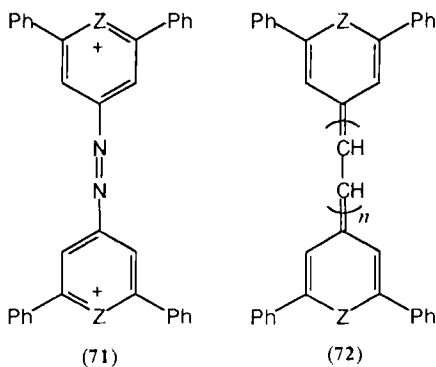
The equilibrium constant for the formation of the radical cation ($K = [\text{55}]^2/[\text{14}][\text{13}]$) has been evaluated as a function of the heteroatom and the α -substituents ($\text{R} = \text{H}, \text{Me}, \text{Ph}$) by the redox potentials [$\log K = (E_2 - E_1)/0.059$]. In all systems the equilibrium is largely displaced toward **55** ($10^3 < K < 10^7$). Redox potentials E_1 and E_2 are both positive in the case of bipyrylium and bithiopyrylium derivatives, and both negative in the case of bipyridinium derivatives. This would explain difficulties encountered in the synthesis of **14** when $\text{Z} = \text{O}, \text{S}$ and **13** when $\text{Z} = \text{NMe}$.

Since Syper and Sucharda-Sobczyk discovered that bipyranlydenes **14** form electrically conductive complexes with electron acceptors (75BAP563), there have been a number of studies on oxidation potentials and conductivities of members of this class [77AG(E)519, 77CC177, 77CC687, 77MI2; 78ANY61; 79JOC880; 81TL2771; 83TL539; 84BSF(2)241; 88MI5]. A systematic investigation of the cyclic voltammetry of **14** ($\text{Z} = \text{O}, \text{S}, \text{Se}, \text{Te}$; $\text{R} = \text{Ph}, \text{Bu}^t, \text{Me}$) in CH_2Cl_2 has been reported by Detty *et al.* (85T4853). Comparing the first oxidation potential, E_1 , the general trend of increasing oxidation potential with increasing size of the heteroatom is maintained throughout the series, indicating that π -overlap of the heteroatom is more important than its electronegativity. Effects of substituents on E_1 are quite dramatic, with a 100- to 200-mV decrease occurring when methyl is substituted for phenyl. The oxidation potential of the radical cation, E_2 , does not appear to have any correlation with the sequential change of the chalcogen atom, but, if "corrected" for the different electron-donating abilities of the chalcogenopyrylium nuclei, follows the trend predicted for the oxidation of a chalcogenopyranly radical, with the telluropyranyl radical oxidizing at the most positive potential

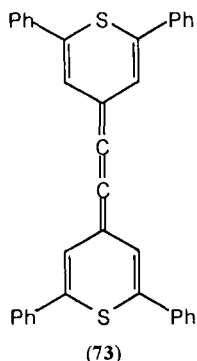
and the pyranil radical oxidizing at the least positive potential (88MI1). Interestingly, the gap between E_1 and E_2 narrows as the size of the heteroatom increases.

Extension of the conjugation between the chalcogenopyranilidene nuclei allows a decrease in energy in removing the second electron from the radical cation, because the dication that is produced encounters less coulombic repulsion. Several insertion types have been investigated to extend the conjugation of these π -frameworks. Hünig and Ruider have carried out a polarographic study of diazavinyllogous bipyrylium, bithiopyrylium, and bipyrydinium **71** (74LA1415). The insertion of a diazo group gives rise to a strong displacement of both E_1 and E_2 toward positive values. In the case of the pyrylium and thiopyrylium derivatives **71** ($Z = O, S$), E_1 and E_2 coalesce in a single polarographic wave, which implies a drastic drop in the stability of the radical cation. Such molecules have the rare electrochemical property of one two-electron reversible oxidation.

The two single-electron waves that are characteristic of **72** ($Z = O, S$) with $n = 0$ (81JHC627) coalesce to one two-electron oxidation wave when $n = 4$ (83JOC2757). Further extension (e.g., $n = 6$) resulted in little change in the cyclic voltammogram. Compound **72** with $Z = S$ and $n = 4$ on one-electron oxidation in CH_2Cl_2 produces a 1:1 mixture of the neutral and the dicationic species and less than 10% of the cation radical species. The presence of this species decreases drastically with the increase of the solvent polarity. Some structural variations, such as benzo fusion and alkylation of the methine carbons, and their effect on the redox potentials have been investigated (84JOC4843).



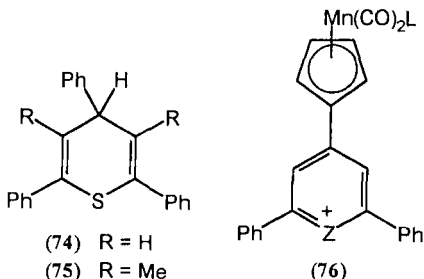
The insertion of cumulenyl double bonds has been also investigated (81CC717, 81CC1143). The cyclic voltammogram of **73** exhibited two reversible one-electron oxidation waves, which resulted in 160 mV more separation than those of **14** with $Z = S$ and $R = \text{Ph}$ (81CC1143; 85T4853).



Reduction and oxidation potentials of chalcogenopyrylocyanines **11** [$Z = Y = O$ ($n = 0-2$), S ($n = 0-3$), Se ($n = 0-3$), NMe ($n = 0-1$)] have been measured by polarography (84MI1). Although the reduction potentials, n being equal, are always increasingly negative as the chalcogen atom becomes lighter, the oxidation potentials do not show a definite trend on changing the heteroatom. Satisfactory correlations have been found between the calculated energy (HMO) of frontier orbitals and the polarographic redox potentials. Reduction and oxidation potentials of **11** ($Z = Y = S$; $n = 0$) have been also determined by cyclic voltammetry (90KGS1480).

Electrochemical oxidation of thiopyrans **74** and **75** to the corresponding thiopyrylium ions proceeds by successive losses of an electron, a proton, and another electron (84KGS318). The same behavior has been shown by 1,2,3,4,5,6,7,8-octahydrothio- and seleno-xanthenes (91KGS47). Electrochemical reduction of 1,2,3,4,5,6,7,8-octahydrothio- and seleno-xanthylium cations has been also investigated (91KGS47).

Polarographic and cyclic voltammetric data were analyzed for Mn complexes **76** ($Z = O, S, NPh, NMe$; $L = PPh_3, CO$). The differences between the half-wave potentials of the first and second reduction steps of **76** were appreciably smaller than those for the corresponding 2,4,6-triphenyl-substituted cations (90MI3).



The electrical conductivity of some charge-transfer complexes in which the acceptor is cation **9** has been measured. With the electron donors *n*-amino-4-(dicyanomethylene)-2,6-dimethyl-1,4-dihydropyridine (77MI1) and *p*-tricyanovinylphenyldicyanomethide ion (80MI4), electrical insulation resulted, whereas with the radical anion of tetracyanoquinodimethane (TCNQ) good electrical conductivity ($\sigma = 8.0 \times 10^{-1} \text{ S cm}^{-1}$) was observed (69JCP377). In the latter work it was also pointed out that the series exemplified by 2,4,6-triphenyl-substituted pyrylium, thiopyrylium, and pyridinium shows a good correlation between the conductivity of the complex TCNQ salt ($\text{S} > \text{O} > \text{NH}$) and the polarizability of the organic cation, the latter being proportional to the λ of the longest-wavelength maximum of the cation.

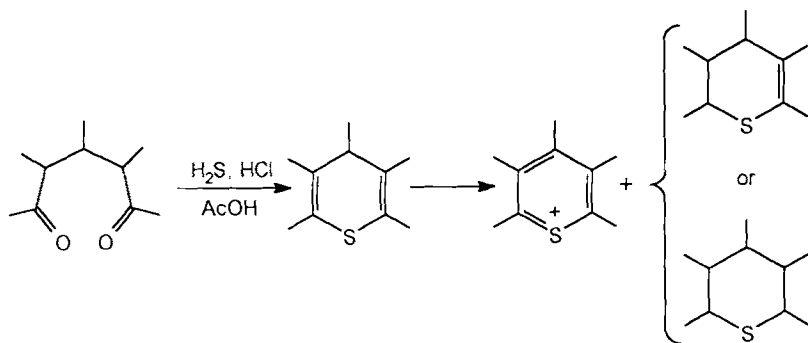
III. Syntheses

A. FROM ACYCLIC PRECURSORS

One-component syntheses of chalcogenopyrylium salts, i.e., those in which the acyclic precursor is a C-5 unit, will be considered first.

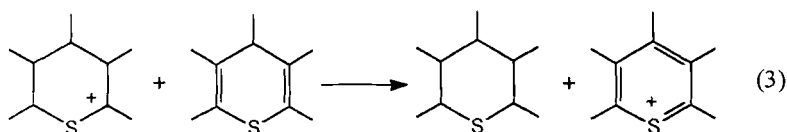
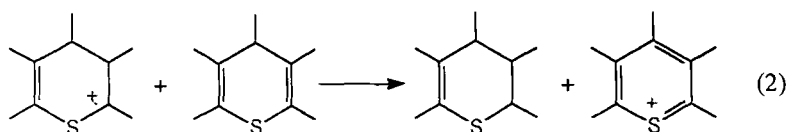
The cyclization of saturated 1,5-pentanediones with H_2S and HCl is one of the most exploited reactions for the synthesis of thiopyrylium salts. These are generally formed together with the corresponding dihydro- or, more frequently, tetrahydro-thiopyrans, as a result of the disproportionation of 4*H*-thiopyran intermediates (Scheme 1). The reaction is frequently performed in AcOH , which appears to facilitate the disproportionation processes (76KFZ80; 81KGS1604).

By performing the reaction in morpholine without added acids, the product of initial addition of H_2S to one of the carbonyl groups has been

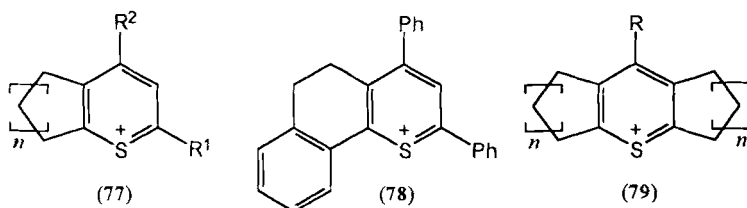


SCHEME 1

isolated. This can be converted to the corresponding thiopyrylium salt by treatment with FeCl_3 or HClO_4 (67ZOR1709). When the reaction is carried out in alcoholic solvents, such as MeOH and EtOH, in the presence of acids, the principal products are thiopyrans (70ZOR193; 72ZOR193, 72ZOR390). The more acidic conditions that are realized in AcOH favor the disproportionation of 4*H*-thiopyran and dihydrothiopyran intermediates. Both disproportionations occur by an initial protonation followed by a hydride abstraction from a second molecule of 4*H*-thiopyran [Eqs. (2) and (3)] (72ZOR193; 81KGS1338; 89RRC509).



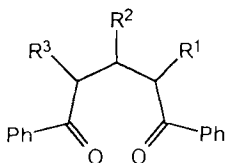
Regarding the thiopyrylium salts prepared by this procedure, they usually have, in the α positions, aryl groups such as phenyl, substituted-phenyl, 2-naphthyl, 2-thienyl, and 2-furyl; in the β positions, hydrogen or methyl; and in the γ position, hydrogen, methyl, or an aryl group. Electron-releasing substituents on the aryl groups, such as methyl or methoxy, favor the formation of thiopyrylium salts. Other interesting thiopyrylium salts that have been prepared by this method are those in which the heterocyclic nucleus is fused with a carbocyclic ring, such as **77** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, Ph , $n = 1, 2$), **78**, **79** ($\text{R} = \text{H}$, $n = 1, 2$; $\text{R} = \text{Me}$, Et , $n = 2$) (68ZOR2054; 70KGS900, 70ZOR1119; 72ZOR193; 74KGS489, 74ZOR1942, 74ZOR2425; 75MI3; 76KFZ80; 77KFZ72; 78ZOR1782; 80KGS1337; 81KGS1604; 82KFZ33, 82KGS708; 85KGS1194; 87MI1).



The pattern of substituents of the diketone affects the reaction course. For example, diketones **80** and **81** are converted only to the corresponding

4*H*-thiopyrans in both MeOH and AcOH, whereas diketone **82** does not react at all in both solvents (70KGS900; 77MI4).

Hydrochloric acid can be replaced by other mineral acids, such as HBr, HI, HClO₄, HBF₄, or by P₂O₅ in inert solvents (70ZOR1119, 70ZOR1513; 73ZOR2434; 75KGS643; 76KFZ80, 76ZOR1802; 81KGS762). The increase of acid strength accelerates the cyclization reaction of 1,5-diketones. For example, **83** reacts with H₂S and HCl in AcOH in 2 days, whereas with HClO₄ the reaction proceeds within 8 hours (77MI3).



(80) R¹ = Me, R² = Ph, R³ = H

(81) R¹ = R³ = Me, R² = Ph

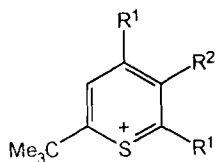
(82) R¹ = R³ = Ph, R² = H

(83) R¹ = R³ = H, R² = Ph

The reaction can be conveniently carried out in CF₃CO₂H. This acid is strong enough to function not only as solvent but also as proton source; it appears to favor the disproportionation of 4*H*-thiopyrans to thiopyrylium ions and tetrahydrothiopyrans (70ZOR1513; 72KGS916, 72ZOR193; 77ZOR443; 80ZOR178; 81KGS1338).

The presence in the reaction mixture of an efficient hydride acceptor appears to favor the conversion of 4*H*-thiopyrans to the corresponding thiopyrylium salts. Thus the thiopyrylium cations **45–48** and **84** have been obtained in fairly good yield by treatment of the corresponding 1,5-pentanediones with H₂S in an acidic medium (Ac₂O, HClO₄) and in the presence of triphenylmethyl cation generated *in situ* by reaction of triphenylmethanol and HClO₄ [85JCR(S)62]).

1,5-Pentanediones can be also transformed to thiopyrylium salts by the action of H₂S and a Lewis acid such as BF₃, AlCl₃, FeCl₃, SnCl₄, and



(84) R¹ = CMe₃, R² = H

(85) R¹ = R² = Ph

SbCl₅ (74ZOR1302, 74ZOR2421; 75KGS643; 79MI4). In the presence of BF₃ · Et₂O, the reaction occurs three to six times faster in AcOH than in Et₂O (74ZOR1302, 74ZOR2421).

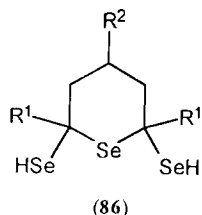
Phosphorus pentasulfide can replace H₂S in the reaction with 1,5-pentanediones yielding thiopyrylium salts with H₂PO₄⁻, H₂PSO₃⁻, and H₂PS₂O₂⁻ as counter-ions. The anions can be subsequently exchanged by treatment with a mineral acid. The reaction can be performed in AcOH or inert solvents (xylene, toluene, dioxane, etc.), or by fusion of the reactants. Depending on the reaction conditions, 4*H*-thiopyrans may be the only product [66ZOR1122; 68URP216747; 71KGS(S)73, 71KGS(S)79; 72KGS1196; 77MI4; 81KGS762]. Reaction with P₄S₁₀ can also be successful when reaction with H₂S and HX fails. Thus cation **85** is obtained in good yield by reaction of the corresponding diketone with P₄S₁₀ in boiling dioxane, whereas with H₂S and HX (X = Cl, ClO₄) in AcOH, the reaction is unsuccessful (81KGS762).

The reaction of 1,5-pentanediones with P₄S₁₀ in AcOH leads to higher yields of thiopyrylium salts when carried out in the presence of alkali or alkaline earth perchlorates, LiClO₄ being the most effective salt. The procedure has been illustrated by the preparation of the 2,6-diphenylthiopyrylium ion (**18**) and analogous derivatives having alkyl or alkoxy groups as *para* substituents of the α -phenyl rings (84SC775). The same procedure has been applied to the synthesis of corands **34** and **35** (91T1977).

In a recent patent it is reported that 1,5-pentanediones are conveniently converted into the corresponding thiopyrylium salts by using 10–20% molar excess zinc sulfide, as the sulfur source, in 6–7 *N* hydrochloric acid in MeOH, EtOH, or Et₂O–AcOH, followed by conversion of the resulting thiopyrylium chlorozincates to fluoroborates or perchlorates with 40% HBF₄ or 57% HClO₄ (92URP1703649).

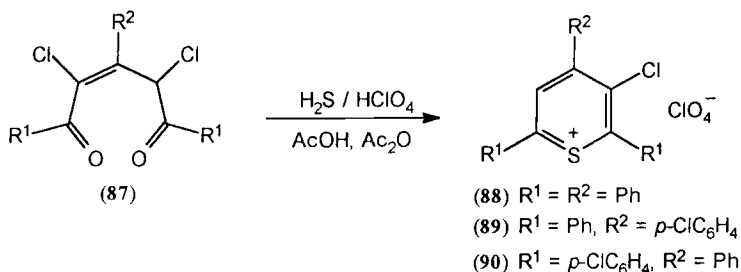
Other successful sulfuration agents are (di)thiocarboxylic acids or dithiophosphoric acid esters (87JAP62-10081).

Analogous to thiopyrylium salts, selenopyrylium salts can be prepared by reaction of 1,5-diketones with H₂Se and HCl in AcOH (73KGS857). The reaction takes place by the initial formation of 4*H*-selenopyrans and/or 2,6-bis(hydroseleno)-1-selenacyclohexanes (**86**) (82ZOR2595; 84KGS1634). The presence of electron-releasing groups favors the formation of 2,6-bis(hydroseleno)-1-selenacyclohexanes. Thus the selenacyclohexanes **86** (R¹ = *p*-MeOC₆H₄, R² = Ph; R¹ = R² = *p*-MeOC₆H₄) have been isolated in the reaction of the corresponding diketones with H₂Se and HCl in AcOH under argon (82ZOR2595). The reaction of 1,5-pentanediones with H₂Se in CF₃CO₂H is rather slow; under these conditions low yield of the selenopyrylium salts **10** and **19** have been

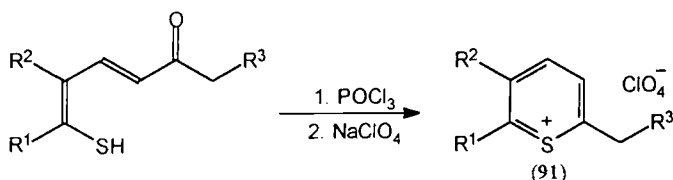


obtained along with significant amounts of the corresponding 2,6-bis-(hydroseleno)-1-selenacyclohexanes and 4*H*-selenopyrans (84KGS1634).

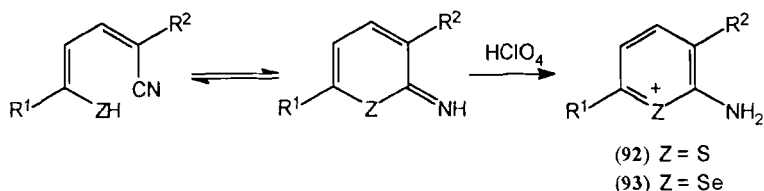
Besides saturated 1,5-diketones, unsaturated 1,5-diketones can also, in some cases, be converted into thiopyrylium salts. The reaction of aryl substituted 2,4-dichloro-2-pentene-1,5-diones (**87**) with H_2S and HClO_4 in a mixture of AcOH and Ac_2O leads to the formation of 3-chlorothiopyrylium perchlorates **88–90**. It should be noted that under the same conditions 1,3,5-triphenyl-2-pentene-1,5-dione is converted quantitatively into the corresponding pyrylium salt **8**. The pentenediones not containing chlorine atoms in the molecule evidently do not react with H_2S under the conditions of acid catalysis as a result of the fact that the cyclization rate for them significantly exceeds the addition rate of H_2S (90ZOR1904).



5-Mercapto-2,4-pentadienones undergo cyclization to thiopyrylium perchlorates **91** by reaction with POCl_3 followed by treatment with a NaClO_4 solution (Scheme 2). In structure **91** both R^1 and R^2 are phenyl or substituted-phenyl groups, whereas R^3 can be H, Me, or Ph (86EGP240745; 89S515).



SCHEME 2



SCHEME 3

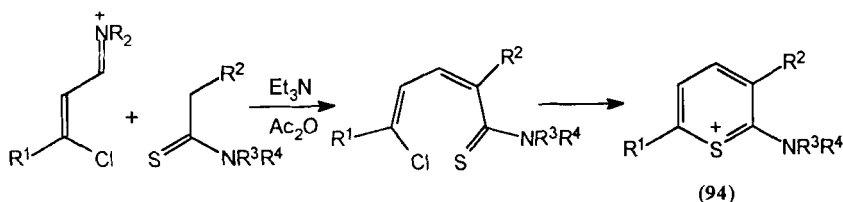
A number of synthetic procedures for the preparation of aminothiopyrylium and selenopyrylium salts has been developed by Liebscher and Hartmann. 2-Aminothiopyrylium salts **92** ($\text{R}^1 = p\text{-MeC}_6\text{H}_4$, $\text{R}^2 = \text{CN}$, CO_2Et , CONH_2) can be prepared by ring-closure of 5-mercapto-2,4-pentadienenitriles in the presence of HClO_4 (Scheme 3) (73ZC342; 74EGP106176).

5-Mercapto-2,4-pentadienenitriles are also intermediates of a one-pot reaction between 5-chloro-2,4-pentadienenitriles and dithiocarbamate anion leading to thiopyrylium salts **92** ($\text{R}^1 = p\text{-MeC}_6\text{H}_4$, 3'-coumaryl, $\text{R}^2 = \text{CN}$, CO_2Et , CONH_2 ; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{CONH}_2$) (74EGP106176; 76JPR705; 81EGP149365).

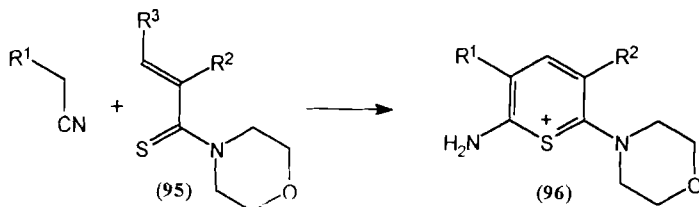
2-Aminoselenopyrylium salts **93** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{CO}_2\text{Et}$, CONH_2 ; $\text{R}^1 = p\text{-MeC}_6\text{H}_4$, $\text{R}^2 = \text{CONH}_2$) have been prepared by reaction of the corresponding 5-chloro-2,4-pentadienenitriles with NaHSe or Na_2SeSO_3 followed by treatment with HClO_4 without the isolation the 5-hydroseleno-2,4-pentadienenitrile intermediate (77EGP126308, 77T731).

2-Aminothiopyrylium salt **92** with $\text{R}^1 = p\text{-MeC}_6\text{H}_4$ and $\text{R}^2 = \text{CN}$ has been also prepared by treatment of the corresponding 5-dimethylamino-2,4-pentadienethioamide with HClO_4 in AcOH . The dimethylamino group is lost in the course of the reaction (76JPR705).

2-Aminothiopyrylium salts have been prepared also by two-component syntheses. The reaction of 3-chloropropenimmonium perchlorates and N,N-disubstituted thioacetamides yields 5-chloro-2,4-pentadienethioamides as probable intermediates that undergo cyclization to thiopyrylium salts **94** ($\text{R}^1 = \text{Ph}$, $p\text{-MeC}_6\text{H}_4$, $p\text{-MeOC}_6\text{H}_4$, $p\text{-ClC}_6\text{H}_4$, $\text{R}^2 = \text{H}$, Ph , $\text{NR}^3\text{R}^4 = \text{piperidino}$, morpholino) (Scheme 4) (71JPR1113; 72BRP1281456, 72GEP2058382).



SCHEME 4



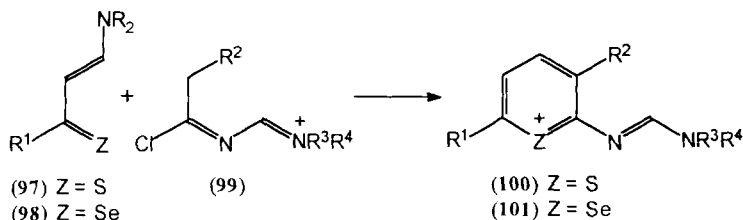
SCHEME 5

2,6-Diaminothiopyrylium salts **96** have been prepared according to Scheme 5, by condensation of 3-functionalized thioacrylamides **95** ($R^2 = \text{Ph}$, $p\text{-ClC}_6\text{H}_4$, $p\text{-PhC}_6\text{H}_4$, 1-naphthyl; $R^3 = \text{NMe}_2$, OH pyrrolidino) with substituted acetonitriles ($R^1 = 2\text{-benzimidazolyl}$, CO_2Et) (83EGP159639, 83ZC403).

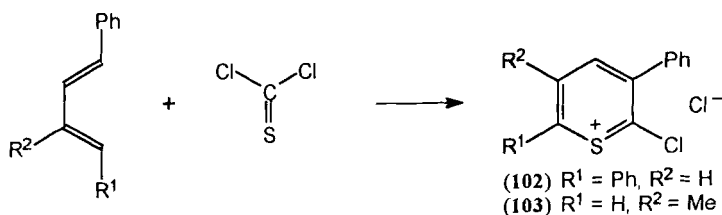
Condensation of β -aminovinylthioketones **97** and cyanoacetic acid derivatives (NCCH_2COR , $R = \text{NH}_2$, OEt) gives 5-mercapto-2,4-pentadienenitriles, which yield thiopyrylium salts **92** ($R^1 = \text{Ph}$, $p\text{-MeC}_6\text{H}_4$, β -naphthyl, $R^2 = \text{CONH}_2$, CO_2Et) according to Scheme 3 (76JPR705). An analogous reaction is given by β -aminovinylselenoketones **98**, which condense with cyanoacetic acid derivatives to yield 2-aminoselenopyrylium salts **93** (77EGP126308, 77T731).

The reaction of 3-chloropropeneimmonium perchlorates with either Na_2S or $\text{Na}_2\text{S}_2\text{O}_3$ yields sulfides of formula $\text{S}(\text{CR}^1=\text{CH}-\text{CH}=\text{N}^+\text{R}_2)_2$, which condense with cyanoacetic acid derivatives to yield thiopyrylium salts **92** ($R^1 = \text{Ar}$, $R^2 = \text{CONH}_2$, CO_2Et , CN) through the intermediacy of 5-mercapto-2,4-pentadienenitriles (74ZC189; 76JPR705).

2-Aminomethyleneamino-thiopyrylium (**100**) (75EGP113911) and -selenopyrylium (**101**) salts (77EGP123527, 77T731) have been prepared by heating formamidine derivatives **99** and β -aminovinylthioketones **97** or selenoketones **98**, respectively (Scheme 6). In structures **100** and **101**,



SCHEME 6



SCHEME 7

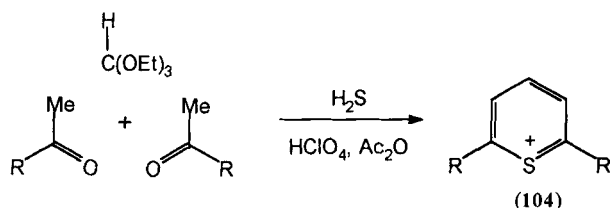
both R^1 and R^2 are phenyl or substituted-phenyl groups, whereas NR^3R^4 can be NMe_2 , pyrrolidino, piperidino, and morpholino.

2-Morpholino-6-aminomethyleneamino-thiopyrylium salts have been prepared by condensation of **95** ($\text{R}^2 = \text{Ph}, p\text{-ClC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, \text{R}^3 = \text{NMe}_2$) and **99** ($\text{R}^2 = \text{Ph}, p\text{-ClC}_6\text{H}_4, \text{R}^3 = \text{R}^4 = \text{Me}$) (83ZC403).

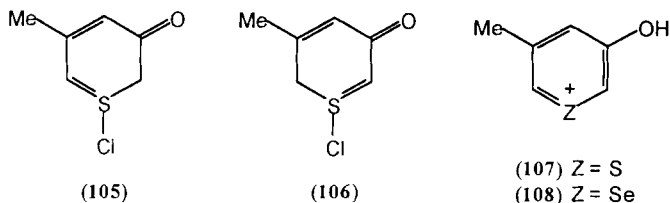
The preparation of 2-chlorothiopyrylium salts can be accomplished by a two-component synthesis. Reaction of *trans-trans*-1,4-diphenyl-1,3-butadiene with excess thiophosgene gives 2-chloro-3,6-diphenylthiopyrylium chloride **102** in high yield (Scheme 7) (67ZC227). The reaction probably consists in a Diels-Alder cycloaddition, followed by elimination of HCl and hydride abstraction. When the reaction was carried out with 1-phenyl-3-methyl-1,3-butadiene, the 3,5-disubstituted thiopyrylium **103** was isolated without evidence of the 4,6-disubstituted regioisomer (84AP938).

Three-component syntheses of thiopyrylium salts are extremely rare. Doddi and Ercolani reported the preparation of 2,6-disubstituted thiopyrylium salts **104** ($\text{R} = \text{Bu}^t, \text{Ph}, p\text{-MeC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4$) in low yield (18–27%) by reaction of methyl ketones and excess triethyl orthoformate in an acidic medium (HClO_4 in Ac_2O) under a H_2S stream (Scheme 8) (85S789). Despite the low yields the reaction is useful, because type **104** salts are not easily accessible.

An early report on the condensation of 2 mol of acetone and 1 mol of thionyl chloride suggested the formation of a compound of structure **105** or **106** (35CB1810). The actual structure of this compound should be that



SCHEME 8



of the chloride of the thiopyrylium **107**. Analogously, condensation of acetone and selenium oxychloride presumably afforded the chloride of the selenopyrylium **108** (65DIS1923).

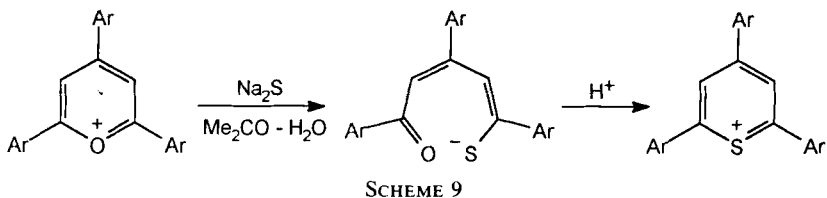
B. FROM CYCLIC PRECURSORS

Syntheses from chalcogenopyrylium ions proceeding with retention of the original chalcogenopyrylium ring will be described in Section IV.

1. Syntheses from Pyrylium Salts

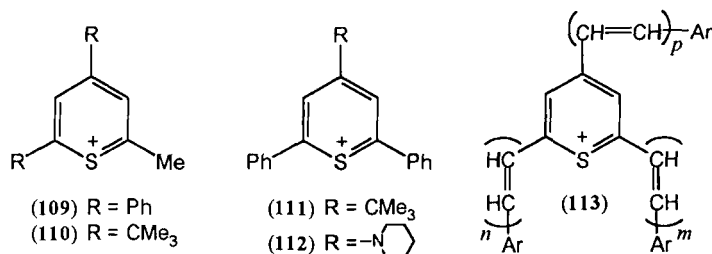
The reaction of pyrylium salts with sodium sulfide in aqueous acetone, proposed by Wizinger and Ulrich as early as 1956, is still one of the most useful method for the preparation of 2,4,6-triarylthiopyrylium salts (56HCA207). It was the first general method allowing access to a large variety of compounds of this class. Electron-releasing substituents on the aryl groups, including the dimethylamino group, cause no problems, and also the presence of halogens is permissible. Accordingly, a large variety of thiopyrylium salts with different substitution patterns and counterions has been prepared (56HCA207; 62JA2090; 63NKZ432; 70BCJ3101; 71JOC791; 92CJC2390). The reaction proceeds through the intermediate formation of a deeply colored (yellow to blue-red) acyclic keto-thioenolate anion, which, on acidification, undergoes cyclization to a thiopyrylium cation precipitating in the aqueous medium (Scheme 9) (56HCA207).

Mislow and co-workers pointed out that thiopyrylium salts prepared according to this procedure can be contaminated by the starting pyrylium cation (75JA2718). Sometimes the contaminated thiopyrylium salt can be

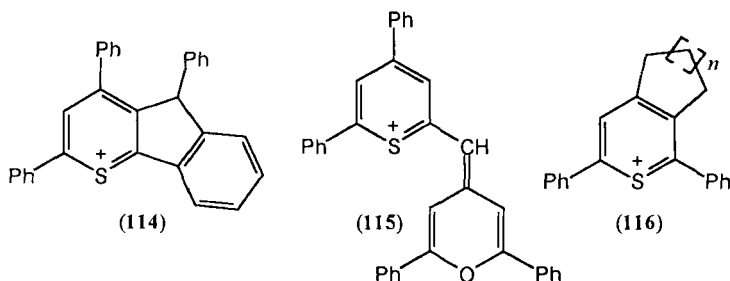


purified by recrystallization (75JA2718). Alternatively, the thiopyrylium content of the mixture can be raised by repeating the reaction on the crude [86JA3409; 87JCS(P2)1427]; in most of the cases a single repetition is sufficient to obtain the pure thiopyrylium salt. A purification procedure relying on the selective addition of a calculated amount of methoxide ion to the contaminating pyrylium salt also proved to be effective [85JCR(S)62, 85S789; 86JA3409].

The reaction with Na_2S has been applied with success to obtain thiopyrylium salts other than 2,4,6-triaryl substituted; for example, the following thiopyrylium cations have been prepared: 2-methyl-4,6-diphenylthiopyrylium (**109**) (56HCA217), 2,6-diphenyl-4-*tert*-butylthiopyrylium (**111**) [87JCS(P2)1427]; 2,6-di-*tert*-butyl-4-(*m*-chlorophenyl)thiopyrylium (**44**) (86JA3409); 2,6-diphenyl-4-(*N*-piperidino)thiopyrylium (**112**) (72JHC783); vinylene homologous of 2,4,6-triarylthiopyrylium [**113** ($m = 1, n = p = 0$; $m = n = 0, p = 1$; $m = n = 1, p = 0$)] (56HCA207); indeno[1,2-*b*]thiopyrylium (**114**) (59JCS55); and pyranilydenemethylthiopyrylium salts [**11** ($Z = \text{S}, Y = \text{O}, n = 0$), **12** ($Z = \text{S}, Y = \text{O}, n = 0$), and **115** [57AC(P)189; 72JHC1105].



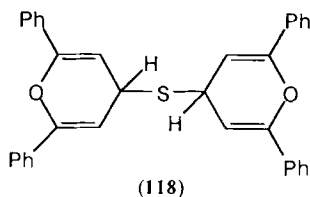
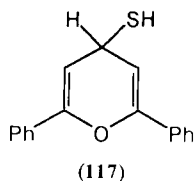
2,4,6-Trialkylpyrylium ions usually do not undergo the $\text{O} \rightarrow \text{S}$ exchange; for example, 2,4,6-tri-*tert*-butylpyrylium ion was recovered unaltered when the reaction was attempted (85UPI). However, the use of NaHS instead of Na_2S has allowed the preparation of 2,4-di-*tert*-butyl-6-methylthiopyrylium (**110**) (85MI3; 87KGS760). Sodium hydrogen sulfide



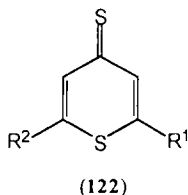
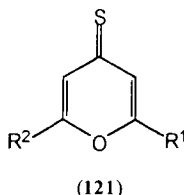
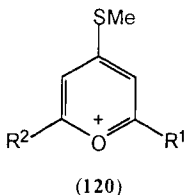
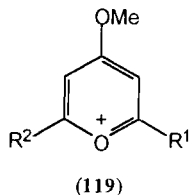
has been also conveniently employed for the preparation of 2-methyl-4,6-diphenylthiopyrylium (**109**) (75S638) and of cations **116** ($n = 1,2$) (84KGS451).

A variant that makes use of Na_2S in $\text{EtOH-Pr}^i\text{OH}$ in the presence of anhydrous Na_2SO_4 has allowed the preparation of 2,6-di-*tert*-butylthiopyrylium ion (**26**) [90ZN(B)701], which had not been accessible by the standard procedure (85UP1).

2,6-Diphenylpyrylium ion (**17**) reacts with sodium sulfide in an aqueous ethereal medium to give the γ -pyranthiol **117**. On being heated in inert solvents, **117** splits off hydrogen sulfide and is converted into the γ -pyranthioether **118** (72KGS1313). However, doubts have been advanced on the correctness of structure **118** [82AHC(S)46].



When good leaving groups are present in the pyrylium ring, a nucleophilic aromatic substitution usually occurs instead of, or in addition to, the $\text{O} \rightarrow \text{S}$ exchange. Thus pyrylium cations **119** ($\text{R}^1 = \text{Me, Ph}$, $\text{R}^2 = \text{H, Me, Ph}$) and **120** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H, Me, Ph}$; $\text{R}^1 = \text{R}^2 = \text{Me}$) react with HS^- or with S^{2-} in cold aqueous solution to give the corresponding 4*H*-pyran-4-thiones **121** as a result of the substitution of the group in γ position [56AC(R)821; 60BCJ1467]. If the reaction with sodium sulfide is carried out in boiling aqueous solution, or in aqueous acetone, the initially formed pyranthione **121** undergoes the $\text{O} \rightarrow \text{S}$ exchange to yield the corresponding 4*H*-thiopyran-4-thione **122** [56AC(R)821].



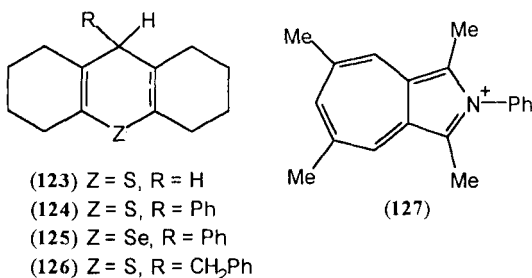
An attempt to prepare 2,4,6-triphenylselenopyrylium cation (**10**) by reaction of the corresponding pyrylium ion **8** with Na_2Se was unsuccessful (78AP170).

2. Syntheses from Chalcogenopyrans

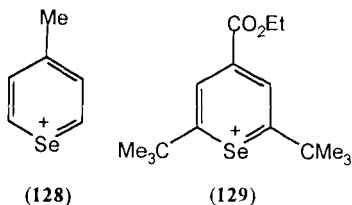
In this section are described the various processes allowing the oxidation of chalcogenopyrans to chalcogenopyrylium ions, with the exception of the processes of hydride transfer between chalcogenopyrans and chalcogenopyrylium ions, described in Section IV,C,8.

Thiopyrylium cations can be easily obtained by oxidation of the corresponding *2H*- or *4H*-thiopyrans possessing at least a hydrogen atom in 2 or 4 position, respectively. Accordingly the unsubstituted thiopyrylium ion (**2**) has been obtained in high yield by oxidation of *4H*-thiopyran with phosphorus pentachloride (63TL1167; 64G203), triphenylmethyl perchlorate (64G203), chlorine, and iodine (65TL2941). In contrast with chlorine and iodine, bromine reacts with *4H*-thiopyran to give the product of electrophilic addition, namely 2,3,5,6-tetrabromothiacyclohexane (65TL2941).

A further example of conversion of a thiopyran into a thiopyrylium salt is offered by compound **123**, which has been oxidized to the corresponding thiopyrylium cation **79** ($R = H$, $n = 2$) by triphenylmethyl chloride, tropylium tetrafluoroborate, silver nitrate, and 1,3,5,7-tetramethyl-2-azoniaazulene (**127**) (74IZV1831).



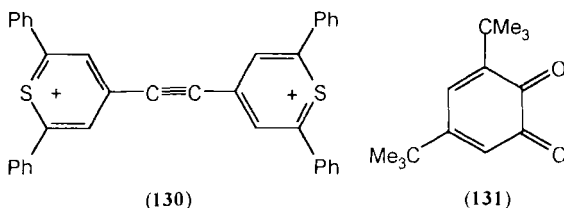
Selenopyrans can be analogously oxidized, thus selenopyrylium ions **3**, **128**, and **129** have been prepared by oxidation of the corresponding *4H*-selenopyrans with PCl_5 or Ph_3CClO_4 [64G203; 67MI1; 90AG(E)424].



Triphenylmethyl cation with ClO_4^- , BF_4^- , or I^- as counter-ion is the reagent most frequently used to convert thiopyrans into thiopyrylium

salts. Accordingly a large number of variously substituted thiopyrylium salts have been obtained from the corresponding *2H*- or *4H*-thiopyrans [67MI1; 72CR(C)677; 73AC(R)563; 74JA6119; 75CR(C)(28)119, 75T3059; 79JA5059; 80MI5]. Analogously, 4,4'-bithiopyrylium dication [**13** (*Z* = S, *R* = H)] (71TL3999) and bis-(2,6-diphenylthiopyrylium-4-yl)-ethyne dication (**130**) (81CC1143) have been obtained from the corresponding bis-*4H*-thiopyran and bis-*2H*-thiopyran, respectively. Triphenylmethyl cation can be also generated *in situ*, by addition of a strong acid to triphenylmethanol; for example, 2,6-diphenylthiopyrylium cation (**18**) has been prepared by treating the corresponding *2H*-thiopyran and triphenylmethanol with trifluoroacetic acid (79JOC4456).

In some cases, instead of abstracting the hydride ion, triphenylmethyl cation favors the loss of the geminal group, thus chalcogenopyrans **124** and **125** lose the phenyl group on treatment with Ph_3CClO_4 to give the corresponding 4-unsubstituted cations. Removal of hydride from **124** and **125** is conveniently performed by the benzoquinone **131** (91KGS51).

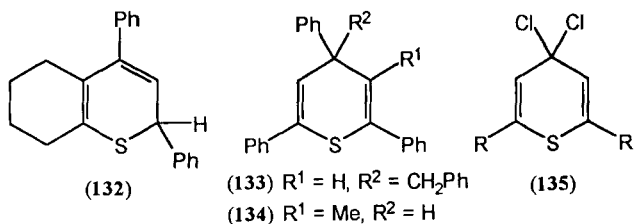


As described in Section III,A, *4H*-thiopyrans disproportionate in acidic media to yield thiopyrylium ions and dihydrothiopyrans or, more frequently, tetrahydrothiopyrans, through the intermediacy of protonated species. Although in some cases good conversions to thiopyrylium ions have been reported (81KGS762), this method is intrinsically limited by the fact that only part of the starting thiopyran is converted to thiopyrylium. However, when the process is carried out in the presence of oxygen, the yield of thiopyrylium ion increases remarkably (79KGS562; 81KGS405). In this case thiopyran radical cations have been suggested as reaction intermediates (83KGS1689). A great number of thiopyrans [67ZOR1344; 70KGS338; 71KGS422, 71KGS(S)76, 71ZOR613; 72KGS1196; 73KGS196; 74ZOR2462; 79KGS562; 80KGS324; 81KFZ38; 83KGS200; 91KGS181] and selenopyrans (81KGS640; 82MI6; 84KGS1634) have been converted into the corresponding cations by treatment with a strong acid, alone or in conjunction with molecular oxygen.

In some cases the proton itself behaves as an oxidant. Thus the formation of 2,6-di-*tert*-butylchalcogenopyrylium ions (**25–28**) and 2,6-diphenyltelluropyrylium ion (**20**) is accompanied by hydrogen evolution

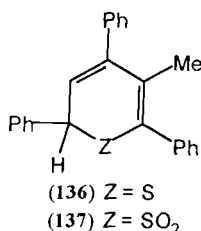
when the corresponding 4*H*-pyrans are heated in the presence of hexafluorophosphoric acid in AcOH (88MI4). 2*H*-Thiopyran **132** disproportionates with 60% HClO₄ at elevated temperature to a mixture of thiopyrylium cation **77** (R¹ = R² = Ph, *n* = 2) and the corresponding tetrahydrothiopyran; however, 70% HClO₄ causes pure oxidation of **132** to **77** [71KGS(S)85].

Perchloric acid can also promote the loss of the benzyl group from 4-benzyl-4*H*-thiopyrans; thus **133** when treated with HClO₄ yields 1,3-diphenylnaphthalene along with a small amount of cation **9** (64LA183). Thiopyran **126** yields thiopyrylium **79** (R = H, *n* = 2) along with isomerization products (73ZOR2177; 79KGS1470). The reported conversion of 4*H*-thiopyrans **135** (R = H, Ph, MeS) to the corresponding 4-chlorothiopyrylium perchlorates by treatment with HClO₄ (68CB3990; 75CB2397) is not an oxidation process. Since thiopyrans of the type **135** are best described as 4-chlorothiopyrylium chlorides (68ZC171), the reaction rather consists in an anion exchange forced by the lower solubility of the perchlorates. Analogously, 2*H*- and 4*H*-chalcogenopyrans possessing hydroxy, alkoxy, mercapto, alkylthio, amino, and alkylamino groups in the 2 and 4 position, respectively, under the action of strong acids, undergo the dissociation into chalcogenopyrylium salts and protonated forms of the above groups; of course these processes are also not oxidations, they are the reverse of nucleophilic addition to chalcogenopyrylium salts driven in the opposite direction by the action of strong acids (Section IV, C, 3-6).



Rather surprisingly 2,4,6-triphenyl-4*H*-thiopyran (**74**) is oxidized to the corresponding thiopyrylium **9** by alkylating agents, such as methyl iodide, dimethyl sulfate, and triethyloxonium fluoroborate (62JA2090).

Hydrogen peroxide usually oxidizes 2*H*- as well as 4*H*-thiopyrans to the corresponding sulfones (62JA2090; 83AHC145); however, the thiopyrans **74** and **134** reacted with H₂O₂ to yield also the corresponding thiopyrylium salts (85KGS1042). In the course of the oxidation of **134**, part of the substrate is converted into the corresponding 2*H* isomer **136**, which is oxidized to the sulfone **137**.

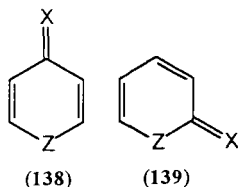


Potassium permanganate in acetone or acetonitrile oxidizes *4H*-thiopyrans and *4H*-selenopyrans to *4H*-thiopyran-4-ones and *4H*-selenopyran-4-ones, respectively (85KGS1489; 91KGS996).

Analogous to 1,5-pentanediones (Section III,A), *4H*-pyrans react with H₂S and HCl in AcOH to yield *4H*-thiopyrans that in the acidic medium can disproportionate to yield thiopyrylium salts (75ZOR1540).

3. *Synthesis from Chalcogenopyrans with Exocyclic Double Bonds*

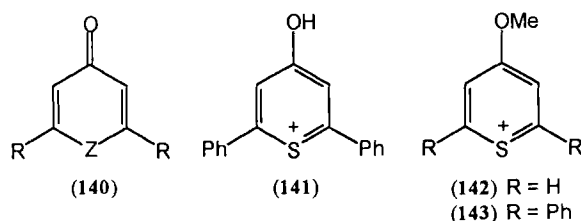
Chalcogenopyrans with exocyclic double bonds, **138** and **139**, can be divided into four main classes depending on the nature of the exocyclic atom or group X, namely chalcogenopyranones (X = O), chalcogenopyranthiones (X = S), chalcogenopyranimines (X = NR), and alkylidenechalcogenopyrans (X = CR₂). Syntheses of chalcogenopyrylium salts from these compounds will be treated in the given order.



Chalcogenopyranones are the conjugated bases of hydroxy-chalcogenopyrylium salts. The faint greenish fluorescence, observed by Arndt and co-workers as early as 1925, of a solution of 2,6-diphenyl-*4H*-thiopyran-4-one [**140** (Z = S, R = Ph)] in conc. sulfuric acid is almost certainly due to the formation of thiopyrylium **141** (25CB1633). The authors also reported the isolation of a chloride salt by treatment of this thiopyran-4-one with HCl, which should be regarded as the chloride of cation **141**. The basicities of some thiopyran-4-ones have been determined spectrophotometrically in H₂SO₄ (68ZOB118).

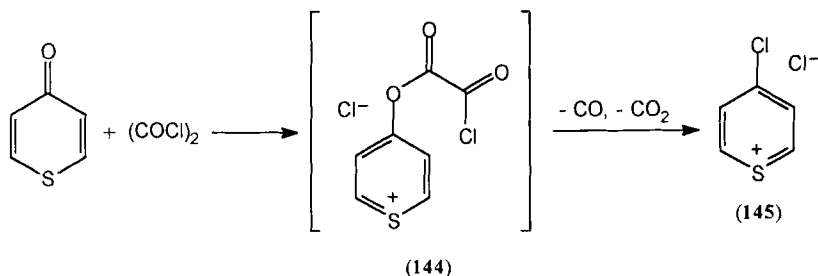
Chalcogenopyranones are weak nucleophiles that can be alkylated to the oxygen atom by powerful alkylating agents; thus thiopyranones **140**

($Z = S$, $R = H$, Ph) react with dimethyl sulfate to give 4-methoxythiopyrylium salts **142** and **143**, respectively [57AC(R)1244; 58CB1224]. Cation **143** has been also obtained by methylation of **140** ($Z = S$, $R = Ph$) with methyl *o*-nitrobenzenesulfonate (63ZOB1864). 2,6-Diphenyl-4*H*-telluropyran-4-one [**140** ($Z = Te$, $R = Ph$)] has been converted to the corresponding 4-ethoxytelluropyrylium salt by reaction with ethyl fluoro-sulfate (82JOC5235).



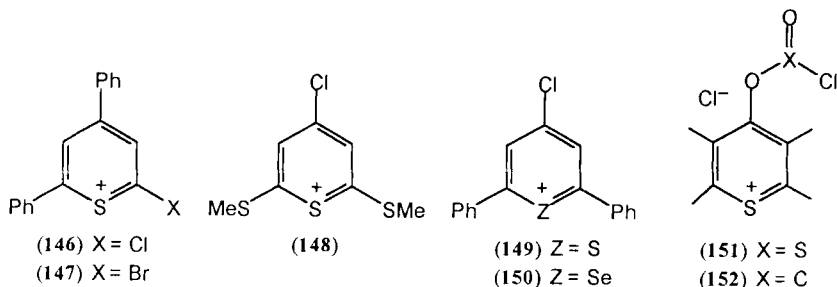
Thiopyran-2- and -4-ones react with oxalyl chloride or bromide to yield 2- and 4-halogenothiopyrylium salts, respectively. The reaction, exemplified for thiopyran-4-one in Scheme 10, probably proceeds through the formation of a nonisolable thiopyrylium ester **144**, which undergoes fragmentation to 4-chlorothiopyrylium (**145**), carbon oxide, and carbon dioxide (68ZC171). Cation **145** and analogous species are present in solution mainly in the ionic form (68ZC171), although the equilibrium with the pyranic form **135** can be affected by solvent polarity (68CB3990). Besides **145**, other thiopyrylium cations have been prepared by this procedure, for example **146–149** [68ZC171; 69JPR61; 84BSF(2)241]. The reaction has proved to be successful also with 2,6-diphenyl-4*H*-selenopyran-4-one [**140** ($Z = Se$, $R = Ph$)], yielding cation **150** [84BSF(2)241].

The reaction of thiopyranones with thionyl chloride (28CB1375; 46JCS604; 68CB346; 75CB2397), and phosgene (68CB3990) to yield chlorothiopyrylium salts probably proceeds, analogously to the reaction with oxalyl chloride, through the formation of the thiopyrylium ester intermedi-

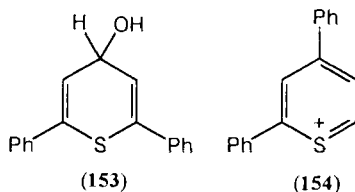


SCHEME 10

ates **151** and **152**, which lose SO_2 and CO_2 , respectively. Another reagent converting thiopyranones into chlorothiopyrylium salts is phosphorus pentachloride (69JPR61). Treatment of a thiopyranone with POCl_3 and an activated aromatic compound can lead to the product of substitution through the intermediacy of the corresponding chlorothiopyrylium ion (83HCA2165) (Section IV,C,7).

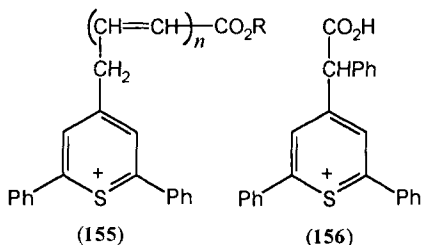


Thiopyran-2- and -4-ones are also weakly electrophilic and can undergo the attack of strong nucleophiles at C-2 and C-4, respectively. The reduction of thiopyran-2- and -4-ones with complex hydrides yields as intermediates thiopyranols (pseudo base), which after treatment with acids lead to thiopyrylium salts unsubstituted at C-2 or C-4, respectively. For example, 2,6-diphenyl-4*H*-thiopyran-4-one [**140** ($\text{Z} = \text{S}$, $\text{R} = \text{Ph}$)] reacts with an excess of LiAlH_4 to give the γ -thiopyranol **153**, which after treatment with HClO_4 in AcOH yields 2,6-diphenylthiopyrylium ion (**18**). Analogously, 2,4-diphenylthiopyrylium (**154**) has been obtained by reaction of the corresponding thiopyran-2-one with LiAlH_4 (in a 4 : 1 molar ratio) followed by acid treatment (70CJC3388). Degani *et al.* carried out the reduction of 4*H*-thiopyran-4-one with AlH_3 to obtain after acidification the unsubstituted thiopyrylium ion (**2**) (63TL1167; 64G203). Surprisingly, the reduction of chalcogenopyran-4-ones **140** ($\text{Z} = \text{O}$, S , Se , Te , $\text{R} = \text{Bu}'$; $\text{Z} = \text{Te}$, $\text{R} = \text{Ph}$) with diisobutylaluminum hydride afforded the corresponding 4*H*-chalcogenopyrans as main products instead of the expected pyranols; there are indications that the reaction proceeds in this case through radical species (88MI4).

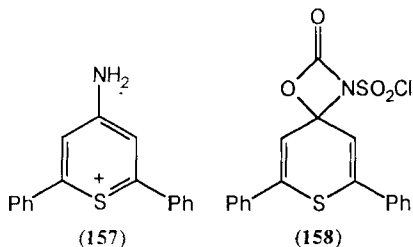


Grignard reagents and lithium alkyls attack the C-4 atom of chalcogenopyran-4-ones to yield the corresponding γ -pyranols that upon acidification

are converted into chalcogenopyrylium salts substituted in the γ position. A selection of chalcogenopyrylium salts prepared by reaction of the corresponding 4*H*-chalcogenopyran-4-one and the appropriate Grignard reagent is represented by structures **23**, **24**, **42**, **49**, and **61–70** (56HCA217; 76JHC1089; 77JHC1399; 86MI2; 88MI1; 92MI2). Reaction of 4*H*-thiopyran-4-one with either methylmagnesium iodide or cyclopentadienylsodium proved to be unsuccessful, the protonated form of the starting thiopyranone being recovered after the acid work-up (65JCS3037). Methylolithium has been used with selenopyranones **140** ($Z = \text{Se}$, $R = \text{Bu}^t$, Me) to obtain 2,6-di-*tert*-butyl-4-methyl- (**63**) [90AG(E)424] and 2,4,6-trimethyl-selenopyrylium cations (74UKZ287), respectively.

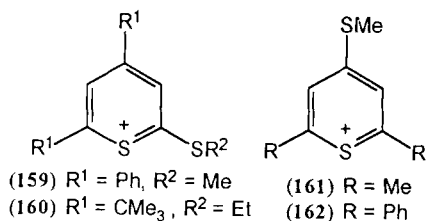


2,6-Diphenyl-4*H*-thiopyran-4-one [**140** ($Z = \text{S}$, $R = \text{Ph}$)] has also been found to undergo the Reformatsky reaction when treated with alkyl esters of α -halogenoacetic acids or γ -bromocrotonic acid in the presence of zinc to give 4-carboalkoxymethyl- (**155**, $n = 0$) or 4-(3-carboalkoxy-2-propenyl)-substituted (**155**, $n = 1$) thiopyrylium derivatives (73KGS1317). Ivanov's reagent [$\text{NaO}_2\text{CCHPhMgCl}$] reacts with 2,6-diphenyl-4*H*-thiopyran-4-one to give, after acidification, thiopyrylium ion **156** (73KGS1317, 73URP382617). The same thiopyranone also reacts with chlorosulfonyl isocyanate to give after acidification the 4-aminothiopyrylium cation **157** (77JHC539). The reaction probably proceeds through the intermediacy of the spiro compound **158** (74JHC195).

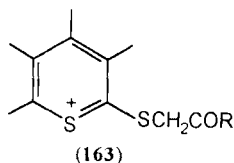


Thiopyranthiones behave similarly to thiopyranones; they can be protonated or alkylated to the exocyclic sulfur to give mercaptothiopyrylium salts [75MI2; 84ZN(A)267] or alkylthiothiopyrylium salts, respectively.

Alkylation of thiopyranthiones occurs more readily than that of thiopyranones. Thus a large number of alkylthiopyrylium salts have been prepared by reaction with alkyl halides, dimethyl sulfate, methyl *o*-nitrobenzenesulfonate, and trialkyloxonium fluoroborates [56AC(R)821; 65LA188; 66KGS183; 67JOC3144, 67LA140; 69JPR61; 73BSF586, 73JPR679; 74BSF1196, 74BSF1356; 76BSF1195, 76JOC818]. Some common alkylthiopyrylium cations prepared from the corresponding thiopyran-2- and 4-thiones are those represented by structures **159**–**162**.

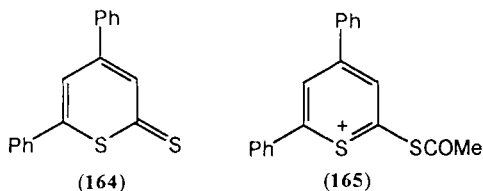


A number of thiopyran-2-thiones have been alkylated with α -halogeno-ketones yielding thiopyrylium cations of the type **163** [74BSF1356; 80BSF(2)427; 84AP938; 86MI3; 87FES465].

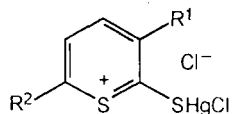


On the analogy of thiopyranones, thiopyranthiones react with oxalyl halides or phosphorus pentachloride to yield halogenothiopyrylium salts. Thus 4,6-diphenyl-2*H*-thiopyran-2-thione (**164**) reacts with oxalyl chloride, and bromide to give cations **146**, and **147**, respectively (69JPR61). The transformation of **164** in **146** has been also carried out with PCl_5 in refluxing toluene [69JPR61; 79JCS(P1)1957]. Treatment of a thiopyranthione with $POCl_3$, PCl_5 and an activated aromatic compound can lead to the product of substitution through the intermediacy of the corresponding chlorothiopyrylium ion [77JCS(P1)1511] (Section IV,C,7).

The thiopyranthione **164** is acetylated by a mixture of Ac_2O and $HClO_4$ giving cation **165** (69JPR61).



Thiopyran-2-thiones undergo mercuration at the exocyclic sulfur atom with HgCl_2 in methanol. By this procedure the mercured cation **166** has been obtained (73BSF586). Mayer *et al.*, treating 2*H*-thiopyran-2-thione with HgCl_2 in MeOH, obtained an adduct whose structure is probably **167** (67LA140). In contrast when the reaction was carried out in water, or with $\text{Hg}(\text{OAc})_2$, 2*H*-thiopyran-2-one was obtained (57CB2362; 67LA140).



(166) $\text{R}^1 = p\text{-MeOC}_6\text{H}_4\text{CO}$,

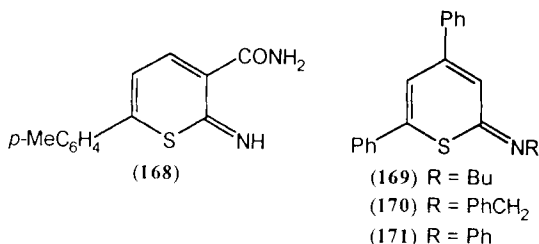
$\text{R}^2 = p\text{-MeOC}_6\text{H}_4$

(167) $\text{R}^1 = \text{R}^2 = \text{H}$

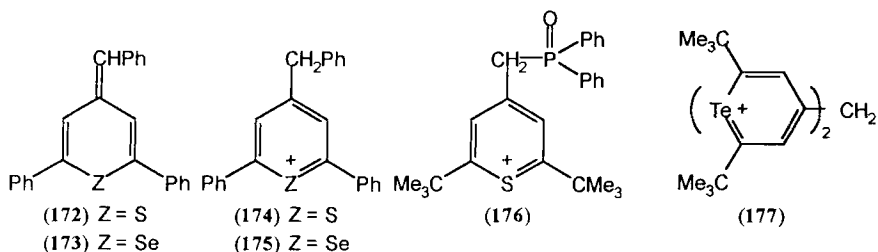
A useful reaction is the treatment of thiopyran-2-thiones with peracetic acid to form 2-unsubstituted thiopyrylium ions. Although the reaction actually involves reduction of the ring system, the exocyclic sulfur atom is oxidized and eliminated as sulfate (70CJC3388; 74CJC3021). For example, 2,4-diphenylthiopyrylium ion (**154**) has been prepared from the thiopyran-2-thione **164**. The reaction does not succeed with thiopyran-4-thiones; thus reaction of 2,6-diphenyl-4*H*-thiopyran-4-thione [**122** ($\text{R}^1 = \text{R}^2 = \text{Ph}$)] with peracetic acid gives the thiopyran-4-one **140** ($\text{Z} = \text{S}$, $\text{R} = \text{Ph}$), instead of 2,6-diphenylthiopyrylium cation (**18**).

From an examination of the literature it would seem that thiopyranthiones, in contrast with thiopyranones, do not usefully react with nucleophilic reagents to give thiopyrylium salts. For example, the reaction of the thiopyran-4-thione **122** ($\text{R}^1 = \text{R}^2 = \text{Me}$) with PhMgBr affords the bithiopyranylidene **14** ($\text{Z} = \text{S}$, $\text{R} = \text{Me}$) (77CC177). This conclusion is also suggested by some patents in which, in order to prepare 2,6-di-*tert*-butyl-4-methylthiopyrylium cation (**62**), the thiopyran-4-thione **122** ($\text{R}^1 = \text{R}^2 = \text{Bu}'$) instead of being directly treated with MeMgI , is first converted to the corresponding thiopyranone **140** ($\text{Z} = \text{S}$, $\text{R} = \text{Bu}'$) (81JAP81-14560, 81JAP81-29586, 81JAP81-30465).

Thiopyranimines have found little use in the preparation of thiopyrylium salts. On the analogy of thiopyranones and thiopyranthiones, they can be protonated or alkylated yielding aminothiopyrylium salts. Thus the thiopyran-2-imine **168** treated with perchloric acid in EtOH is protonated to the nitrogen atom giving the corresponding 2-aminothiopyrylium perchlorate (76JPR705), and thiopyran-2-imines **169–171** are methylated by MeI to the corresponding *N*-methyl thiopyrylium derivatives [69JPR61; 77JCS(P1)1436].

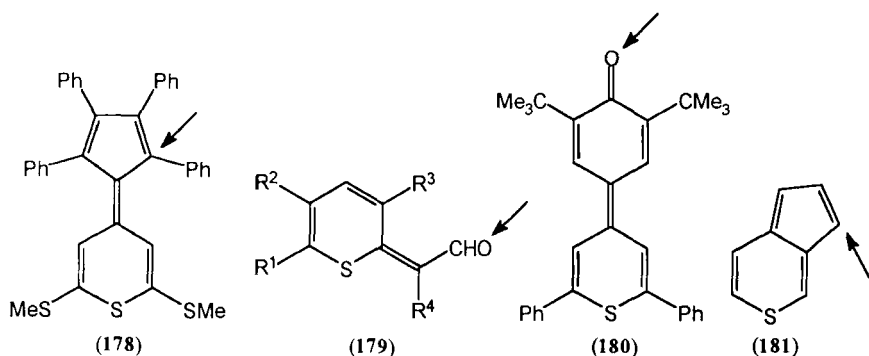


Alkylidenechalcogenopyrans can be protonated at the exocyclic carbon atom yielding the corresponding chalcogenopyrylium ions in a reversible reaction. In fact alkylidenechalcogenopyrans are considered the anhydrobases of chalcogenopyrylium ions possessing alkylic CH groups in positions 2, 4, or 6. Anhydrobases are often unstable unless the exocyclic carbon is bonded to electron-withdrawing groups or groups capable of extending the conjugation of the whole system. The main routes to anhydrobases are via phosphorus derivatives (Section IV,C,6), or via reactions with CH acids (Section IV,C,7). Thus, for example, the 4-benzylidenethiopyran **172** and the seleno analog **173**, prepared from the corresponding chalcogenopyranylphosphonates, can be protonated to yield cations **174** and **175**, respectively (73ZOB359). Analogously cations **176** and **177** have been obtained by protonation of the corresponding anhydrobases (85T811; 89MI2).



In some cases, anhydrobases instead of being protonated at the exocyclic carbon atom are protonated at a vinylogous or phenylogous position. This is shown, for example, by the anhydrobases **178**, **179** [$R^1, R^2, R^4 = \text{Ph, Me}$; $R^3 = \text{H}$; $R^3R^4 = (\text{CH}_2)_3$], **180**, and **181**, where the atom that undergoes protonation is indicated by an arrow (64JA708; 68CB3990; 75CB2397; 89JPR763). Other molecules analogous to **178**, which can be considered sulfur analogs of sesquifulvalene, have been investigated [63CI(L)1559; 69AG(E)478; 72LA93].

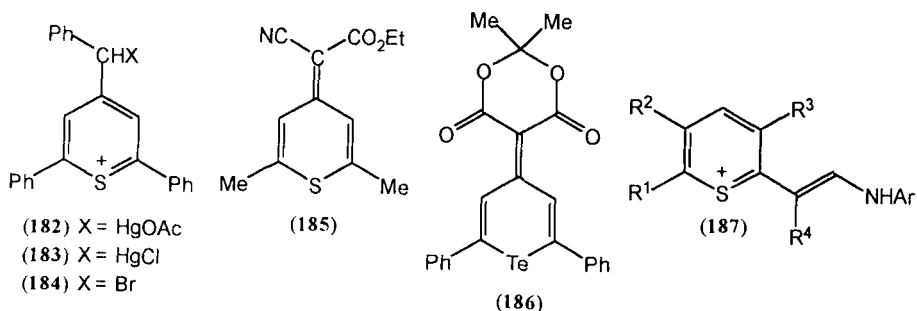
Anhydrobases can react with electrophilic reagents to yield chalcogenopyrylium salts. Often, however, anhydrobases are generated *in situ* by



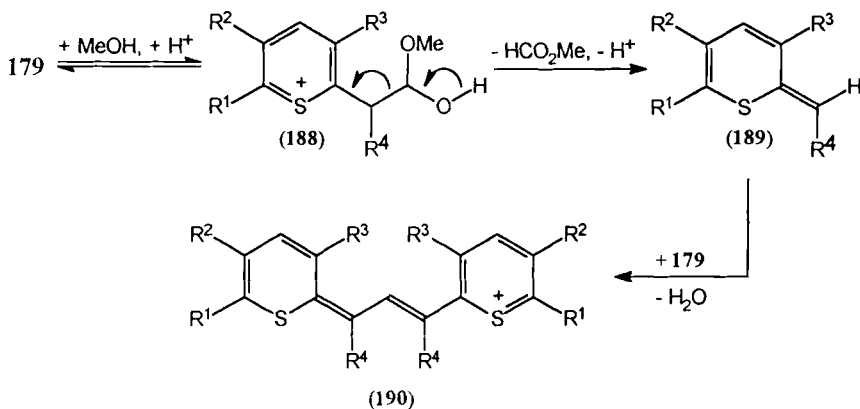
reaction of an alkylchalcogenopyrylium ion with a suitable base. These cases are reviewed in Section IV, B, 1. Here are reported only those preparations starting from preformed anhydrobases. Thus treatment of 4-benzylidenethiopyran **172** with $\text{Hg}(\text{OAc})_2$ (in a 1 : 1 molar ratio) or HgCl_2 (in a 1 : 2 molar ratio) affords the mercurated thiopyrylium salts **182** $\cdot \text{AcO}^-$ and **183** $\cdot \text{HgCl}_3^-$, respectively (77URP541848). The same anhydrobase reacts with bromine in CHCl_3 to yield cation **184** (75URP469695).

Some anhydrobases can give chalcogenopyrylium salts by hydrolysis and decarboxylation in acidic media. Thiopyranylidene **185**, prepared by condensation of 2,6-dimethyl-4*H*-thiopyran-4-one [**140** ($\text{Z} = \text{S}$, $\text{R} = \text{Me}$)] and ethyl cyanoacetate, treated with HClO_4 undergoes hydrolysis and decarboxylation to yield 2,4,6-trimethylthiopyrylium perchlorate (74UKZ287). Analogously telluropyranylidene **186**, obtained by reaction of 4-ethoxy-2,6-diphenyltelluropyranylium and Meldrum's acid in pyridine, when heated in formic acid affords 4-methyl-2,6-diphenyltelluropyranylium ion (82JOC5235).

Anhydrobases **179** have been condensed with a number of *para*-substituted anilines (ArNH_2) to give thiopyrylium salts **187** (84ZC183). The same anhydrobases have been converted, at room temperature in



acidic methanol solutions, to symmetrical 2,2'-thiopyrylotrimethine dyes **190** in nearly quantitative yield. The reaction proceeds through the protonated hemiacetal **188**, which losing a molecule of methyl formate yields the anhydrobase **189**. This condenses in the medium with another molecule of **179** to yield the final product (84ZC146; 89JPR763). The reaction is also successful with the seleno analogs of anhydrobases **179** (84ZC146).

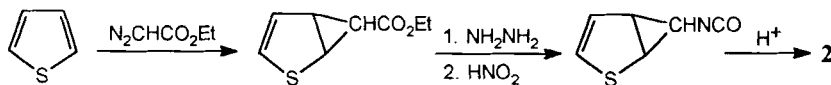


Bithiopyrylium dications **13** can be prepared by oxidation of bithiopyranylidenes **14**. Thus **13** ($\text{Z} = \text{S}$, $\text{R} = \text{Ph}$) has been prepared from the corresponding bithiopyranylidene **14** by oxidation with chlorine or bromine in chlorinated solvents (30CB3121; 73LA1036), or with $\text{Cu}(\text{ClO}_4)_2$ in acetonitrile (69JHC623). Bithiopyranylidene **14** ($\text{Z} = \text{S}$, $\text{R} = \text{Me}$) has been oxidized to the corresponding bithiopyrylium **13** by treatment with HClO_4 in acetone (73LA1036).

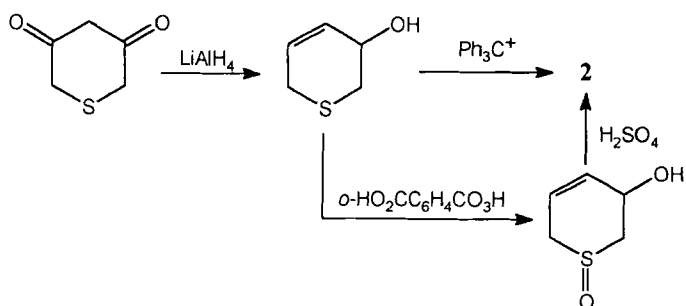
4. Syntheses from Other Cyclic Systems

The first preparation of the unsubstituted thiopyrylium ion (**2**), illustrated in Scheme 11, has been developed by Pettit starting from thiophene (60TL11).

Soon afterward two routes for the preparation of **2** were proposed by Lüttringhaus and Engelhard (61AG218). The two routes, illustrated in Scheme 12, have, as common intermediate, 1-thia-3-cyclohexen-5-ol obtained by LiAlH_4 reduction of 1-thia-3,5-cyclohexandione.



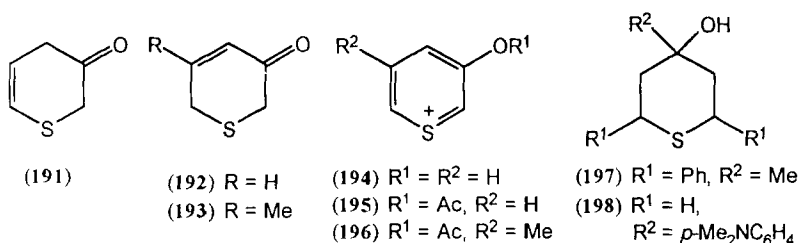
SCHEME 11



SCHEME 12

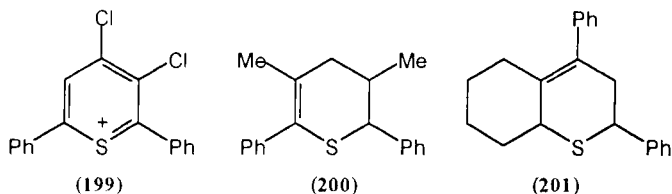
1-Thia-2-cyclohexen-5-one (**191**) and 1-thia-3-cyclohexen-5-one (**192**) can be converted into 3-hydroxythiopyrylium (**194**) by treatment with triphenylmethyl perchlorate in acetonitrile. Analogously **193** is converted into 3-hydroxy-5-methylthiopyrylium ion (**107**). If the reaction is carried out in AcOH–Ac₂O the acetylated thiopyrylium salts **195** and **196** can be obtained. The latter salts can be deacetylated to yield **194** and **107**, respectively, by treatment with trifluoroacetic acid [75JCS(P1)2099].

Triphenylmethyl perchlorate, generated *in situ* by triphenylmethanol and HClO₄, has been reported to oxidize also 2,6-diphenylthiacyclohexane to 2,6-diphenylthiopyrylium cation (**18**), and the thiacyclohexanol **197** to 4-methyl-2,6-diphenylthiopyrylium cation (66HCA2046). The latter oxidation has been also carried out with triphenylmethyl trifluoroacetate generated *in situ* (75S638). The same procedure has been applied to the oxidation of the thiacyclohexanol **198** (76JHC1089).



2,6-Diphenyl-1-thiacyclohexan-4-one reacts with PCl₅ to give a mixture of 4-chloro- (**149**) and 3,4-dichloro-2,6-diphenylthiopyrylium (**199**) chlorides (68ZC171).

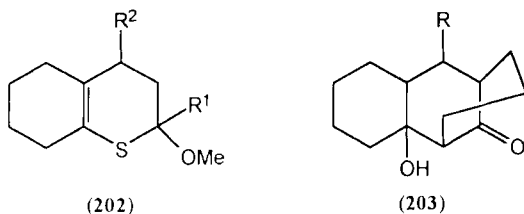
Dihydrothiopyrans **200** and **201** treated with CF₃CO₂H disproportionate to give the corresponding thiopyrylium trifluoroacetates and thiacyclohexanes (Section III,A), showing that the disproportionation of dihydrothio-



pyrans occurs regardless of the location of the double bond (75ZOR2447; 77ZOR443).

The 2-methoxy-dihydrothiopyrans **202** (R^1 , R^2 = aryl groups) react in AcOH with HCl or HClO_4 forming the corresponding tetrahydrothiocromenylium chlorides or perchlorates [77 ($n = 2$)] (70ZOR193).

Treatment of the hydroxyketones **203** ($R = \text{H, Me, Pr, Ph, } p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4$) with H_2S and an acid, e.g., HCl, HClO_4 , $\text{BF}_3 \cdot \text{OEt}_2$, gives the corresponding octahydrothioxanthylum salts **79** ($n = 2$) and perhydrothioxanthenes (78KGS1615).



2,6-Bis(hydroseleno)-1-selenacyclohexanes **86** ($R^1 = \text{Ph}$, $R^2 = \text{H}$; $R^1 = R^2 = \text{Ph}$; $R^1 = p\text{-MeOC}_6\text{H}_4$, $R^2 = \text{Ph}$; $R^1 = R^2 = p\text{-MeOC}_6\text{H}_4$), which are produced in the ring closure of 1,5-pentanediones with H_2Se in acidic media (Section III, A), when treated with acids ($\text{CF}_3\text{CO}_2\text{H}$, or HClO_4 , or $\text{BF}_3 \cdot \text{Et}_2\text{O}$) in benzene, yield the corresponding selenopyrylium cations and selenacyclohexanes, along with selenium (83URP1051089; 84KGS1283, 84KGS1634). The reaction occurs through the intermediacy of 4*H*-selenopyrans.

IV. Reactions

A. ANION EXCHANGE REACTIONS

Replacement of the counterion of a chalcogenopyrylium cation with another is usually carried out to characterize the salt in question; to mod-

ify its physical properties, with particular regard to its stability and solubility; and to get rid of anion that could interfere in a certain application.

The most simple anion exchange reaction is the metathesis reaction; it can be conveniently applied when the solubility of the desired salt is lower than that of the starting one. For example, since thiopyrylium chlorides are usually readily soluble, they can be easily converted into iodides, chloroferrates, and perchlorates (70KGS900).

Owing to the low solubility of most of the chalcogenopyrylium perchlorates, simple addition of HClO_4 generally causes their precipitation (63NKZ432; 87MI3). Indeed it is usual to add perchloric acid at the end of a preparation of a chalcogenopyrylium ion to precipitate the perchlorate salt. Chalcogenopyrylium perchlorates can be readily purified by dissolution in CH_3CN or CH_2Cl_2 and reprecipitation by addition of a large amount of ethyl ether.

In the cases in which the desired salt is not significantly less soluble than the starting one (but consider also that in a different solvent or conditions the solubilities can be reversed), one can exploit the low solubility of the other couple of ions that form in the metathetical reaction, thus leaving in solution the desired chalcogenopyrylium salt. For example, 2,4,6-triphenylthiopyrylium (9) tosylate could be obtained by treating $9 \cdot \text{BF}_4^-$ in EtOH with KOTs, exploiting the low solubility of KBF_4 in EtOH (66NKZ1069). Alternatively, treating the chalcogenopyrylium salt with a suitable nucleophile, one can obtain a neutral adduct that is extracted with an organic solvent and treated with the appropriate acid to restore the chalcogenopyrylium system. By this procedure, using methoxide ion as nucleophile (Section IV,C,3), pyrylium, thiopyrylium, and selenopyrylium salts having as counter-ions HCO_2^- , PhCO_2^- , $\text{HOC}_6\text{H}_4\text{CO}_2^-$ have been prepared (88URP1447824). Another method makes use of ion-exchange resins. Thus exchange of perchlorate, fluoroborate, and hexafluorophosphate anions for chloride has been carried out by treating chalcogenopyrylium salts of the above anions with Amberlite IRA-400 (Cl) ion-exchange resin in methanol solution (90JMC1108, 90USP4916127).

An unusual anion exchange takes place in the reaction between 2,6-diphenylthiopyrylium (18) iodide and tetracyanoquinodimethane (TCNQ) in acetonitrile. The iodide ion undergoes oxidation to iodine, leaving as counter-ion of 18 the radical anion of TCNQ (77TH1). Salts of this type have been also prepared by metathesis (69JCP377).

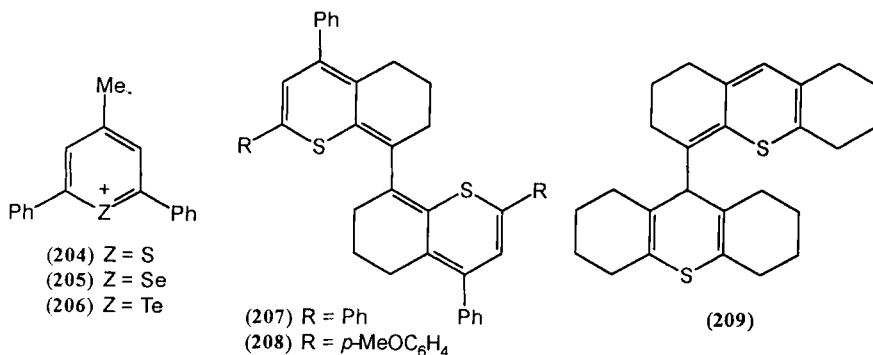
2,4,6-Triphenylthiopyrylium (9) trihalides have been prepared by addition of a solution containing a halogen to a solution of a halide of 9 (65NKZ534).

B. REACTIONS INVOLVING RING SUBSTITUENTS

1. *Reactions of Alkyl Substituents*

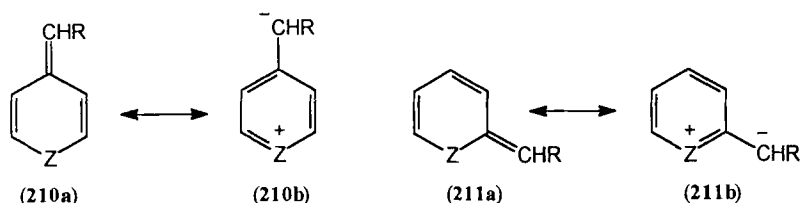
Chalcogenopyrylium salts possessing CH_3 , CH_2R , or CHR_2 groups in α or γ positions easily undergo deprotonation affording α - or γ -alkylidenechalcogenopyrans. Reactions of preformed alkylidenechalcogenopyrans yielding chalcogenopyrylium ions have been described in Section III,B,3.

In some cases alkylidenechalcogenopyrans are not stable under basic conditions. In this respect it has been reported that 2,6-diphenyl-4-methylthiopyrylium ion (**204**) in aqueous acetone in the presence of alkali undergoes oxidation to yield the dimerization product **72** ($\text{Z} = \text{S}$, $n = 1$) (74KGS49). As observed for 4-methyl-flavylium and -thioflavylium ions, it is probable that the oxidant of the anhydrobase is not atmospheric oxygen but the starting cation itself (69TL2047). Analogously, cations of the type **77** ($\text{R}^1 = \text{Ph}$, $p\text{-MeOC}_6\text{H}_4$, $\text{R}^2 = \text{Ph}$, $n = 2$) are oxidized by potassium ferricyanide in alcoholic sodium hydroxide to yield dimers **207** and **208** (87ZOR2019). Dimeric products of this sort are bis-anhydrobases and as such can be protonated to yield bis-thiopyrylium dications (74KGS49; 87ZOR2019). Dimerizations of this type can be also carried out electrochemically (84JOC4843). A different dimerization type is observed by reaction of octahydrothioxanthylum **79** ($\text{R} = \text{H}$, $n = 2$) with pyridine or an aqueous solution of NaHCO_3 in EtOH, the dimer having the structure **209** (89KGS479).

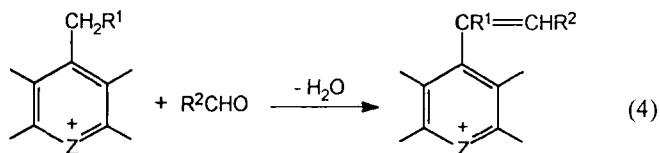


From the kinetics of deuterium exchange of methyl-substituted thiopyrylium salts, it has been concluded that deprotonation of a γ -methyl group occurs faster than that of a α -methyl group. This behavior is analogous to that of methyl-substituted pyrylium salts, although the activating effect of oxygen is greater than that of sulfur (69MI2).

Alkylidenechalcogenopyrans possess an electron-rich exocyclic carbon atom, as suggested by the resonance structures **210b** and **211b**, which is able to react by nucleophilic attack with aldehydes and derivatives, chalcogenopyranones, formamide derivatives, orthoesters, electron-deficient compounds, and other electrophiles, such as tetracyanoethylene, bromine, and nitrosonium ion. The reactions with the above substrates will be described in the given order. Since α - and γ -alkyl chalcogenopyrylium ions show analogous behavior, only the reactions of γ -alkyl chalcogenopyrylium salts will be graphically illustrated, implying that analogous schemes hold for the α -alkyl substituted cations.

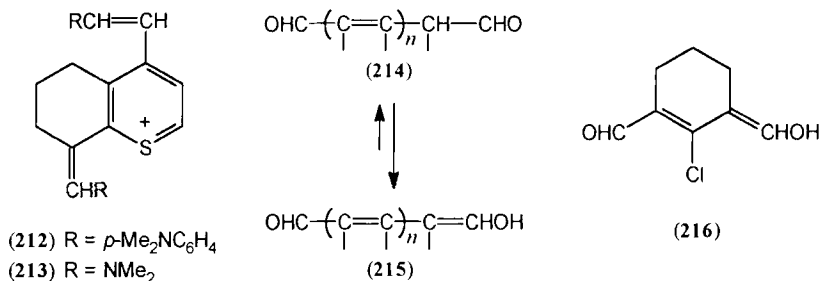


Condensation of alkyl-substituted chalcogenopyrylium ions with aldehydes can be represented by Eq. (4). The reaction is usually carried out by heating the reactants in Ac_2O or in Ac_2O – AcOH mixtures. The aldehydes that have been utilized are more or less extensively conjugated, and major applications of the reaction are found in the synthesis of cyanine dyes incorporating chalcogenopyrylium nuclei at the ends of a polymethine chain. The chalcogenopyrylium salts most utilized in the condensation with aldehydes are the methyl-substituted ones, such as **62–64**, **109**, and **204–206**. Condensation of thiopyrylium salts with aldehydes was first performed by Wizinger and Ulrich, who treated 2-methyl-4,6-diphenyl- (**109**) and 4-methyl-2,6-diphenyl thiopyrylium salts (**204**) with substituted benzaldehydes and cinnamaldehydes (56HCA217). Successively the reaction has been extensively applied, also with the heavier chalcogenopyrylium ions (74KGS53, 74KGS64; 75KGS617; 76KFZ73; 77JOC885; 80JPR543; 81JAP81-29586; 82JOC5235, 82KGS1178; 84JAP59-41363; 85UKZ1198; 87ZC443; 88EGP253428, 88EGP258009, 88MI1; 90JA3845, 90JMC1108).

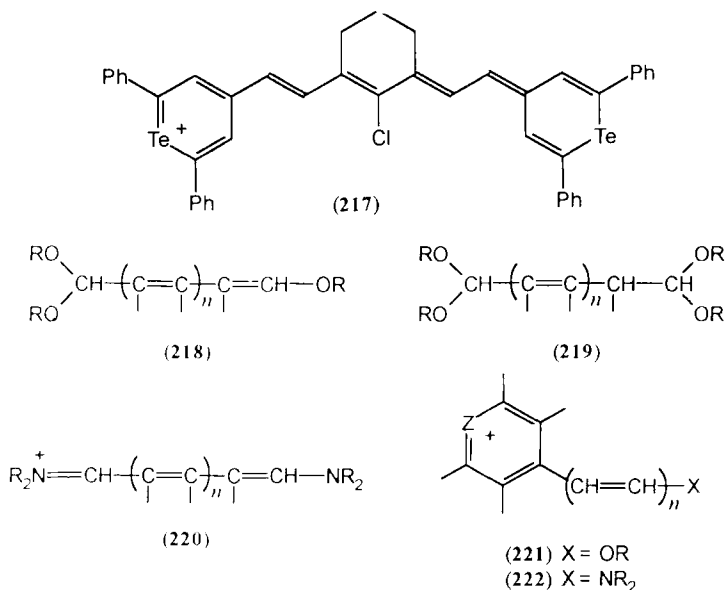


In the presence of two active methyl or methylene groups, the condensation can occur with two equiv. of aldehyde. Thus compound **212** has been

prepared by the condensation of **77** ($R^1 = H$, $R^2 = Me$, $n = 2$) with two equiv. of *N,N*-dimethylaminobenzaldehyde (76KFZ73).

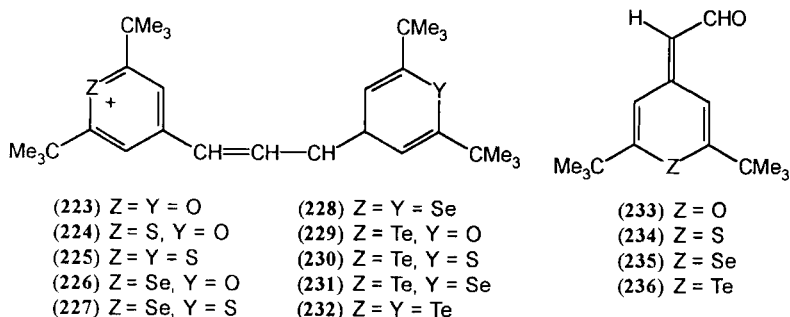


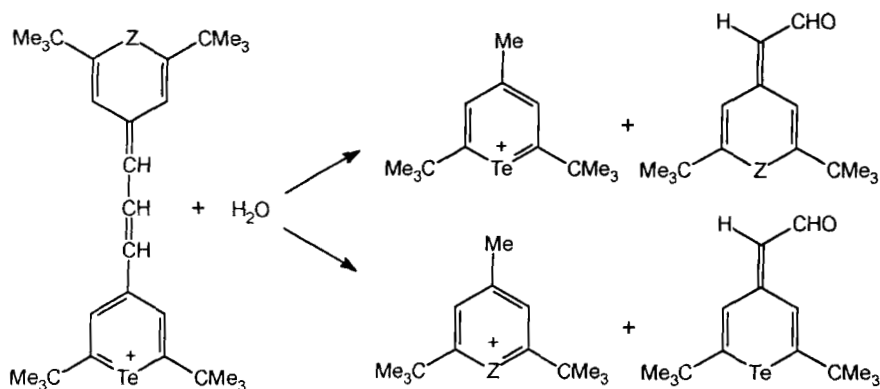
Two equiv. of a chalcogenopyrylium ion can be condensed with 1 equiv. of a bisaldehyde of type **214**, actually present in the conjugated enolic form **215**, to prepare extended polymethine cyanine dyes. For example, by condensation of two equiv. of 2,6-diphenyl-4-methyltelluropirylium (**206**) with one equiv. of the bisaldehyde **216**, the stable bis(telluropirylo)-heptamethine dye **217** has been prepared (82JOC5235). Similar condensations have been also carried out with derivatives of bisaldehydes, such as **218–220**. Condensations of this type are usually carried out in Ac_2O or Ac_2O – AcOH mixtures in the presence of sodium acetate, and probably proceed through the intermediate formation of alkoxypolyenylyl- and aminopolyenylyl-chalcogenopyrylium salts, e.g., **221** and **222**, respec-



tively (74KGS49; 78UKZ838; 81GEP3031595, 81KGS117, 81KGS1195; 82JOC5235; 83KGS1559; 84GEP3316666, 84KGS451; 85UKZ95, 85UKZ1066; 86ZOR170; 87KGS760). Compounds of types **221** and **222** can be prepared independently and condensed with chalcogenopyrylium ions possessing active methyl or methylene groups (74KGS53; 80KGS898; 82KGS1178).

An interesting observation was made by Detty *et al.* in the course of the preparation of the trimethine cyanine dyes **223**–**232** by condensation of 2,6-di-*tert*-butyl-4-methylchalcogenopyrylium cations **61**–**64** and aldehydes **233**–**236** (90JMC1108). Whereas the preparations of symmetrical dyes **223**, **225**, **228**, and **232** are straightforward, the preparations of the unsymmetrical dyes **224**, **226**, **227** and, in particular, **229**–**231** are not as straightforward. Although **224**, **226**, and **227** can be prepared in greater than 98% purity, trace amounts of the symmetrical dyes **223**, **225**, and **228** in appropriate combinations can be detected by ^1H NMR. In preparing the unsymmetrical telluropirylium dyes **229**–**231**, the scrambling of heteroatoms can be extensive to the point that a statistical distribution of all combinations can be isolated. For example, the preparation of **231** from the chloride of selenopyrylium cation **63** and telluropyranylidene aldehyde **236** in Ac_2O gives a 1:2:1 mixture of **228**, **231**, and **232**, respectively. Use of PF_6^- as counter-ion of **63** instead of Cl^- gives less scrambling. Two mechanisms for the scrambling have been considered: the first is a reverse-aldol reaction that can follow either of two routes shown in Scheme 13; the second would involve nucleophilic addition to the α -position of the chalcogenopyrylium ring followed by ring-opening. In the first mechanism scrambling occurs between the two heterocyclic rings, whereas in the second only the scrambling of heteroatoms is involved. The second mechanism has been ruled out by a simple labeling experiment. The ability of telluropirylium dyes to undergo oxidative addition of halogens to give isolable compounds (Section IV,C,2) offers a method of

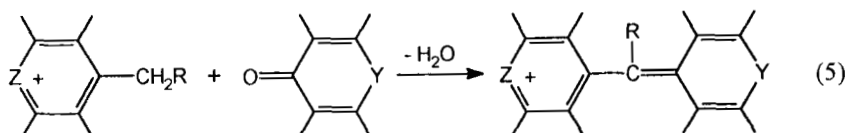




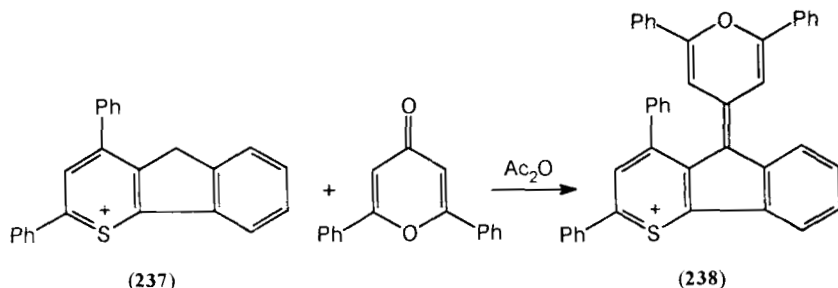
SCHEME 13

purification for unsymmetrical telluropirylium dyes (90JMC1108, 90USP4963669).

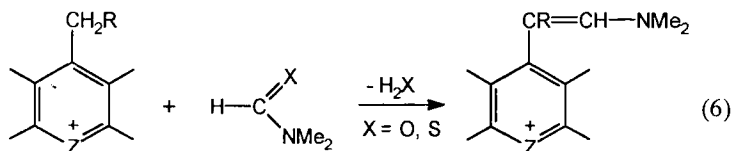
Chalcogenopyrylium salts possessing α - or γ -methyl or methylene groups react with 4*H*-chalcogenopyran-4-ones to yield monomethine cyanine dyes as shown in Eq. (5). Usually the reaction occurs in refluxing acetic anhydride. Various monomethine dyes have been prepared by this procedure with all possible combinations of chalcogens (56HCA217; 66KGS183; 77JHC1399; 78AP170, 78AP236; 82JOC5235, 82KGS1178; 88MI1).



Although, normally, β -alkyl-substituted thiopyrylium salts do not condense with either aldehydes or chalcogenopyranones, it has been reported that the 5*H*-indeno[2,1-*b*]thiopyrylium ion **237** reacts with 2,6-diphenyl-4*H*-pyran-4-one to yield the condensation product **238** (77JHC119).

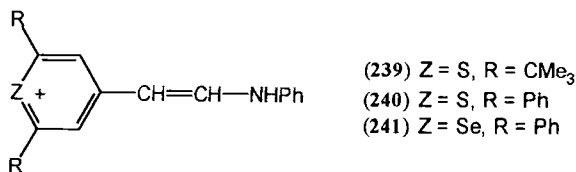


Chalcogenopyrylium salts with active methyl or methylene groups react readily with dimethylformamide or thioformamide in hot acetic anhydride to give α - or γ -(*N,N*-dimethylaminovinyl)chalcogenopyrylium salts as shown in Eq. (6) (76KFZ73; 81KGS1195; 82JOC5235).

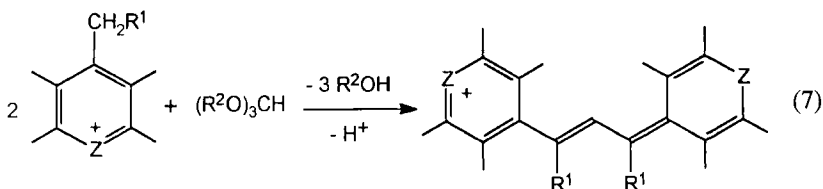


In the presence of two of these active groups, the condensation can occur with two equiv. of dimethylformamide; thus compound **213** has been prepared from **77** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $n = 2$) (76KFZ73). *N,N*-Dimethylaminovinyl-chalcogenopyrylium salts can be hydrolyzed in aqueous acetonitrile in the presence of alkali to afford chalcogenopyranylidene acetaldehydes, e.g., **236** (81KGS1195; 82JOC5235). Aminobutadienylthiopyrylium salts have been hydrolyzed under analogous conditions (87ZC443; 88EGP253428).

Diphenylformamidine reacts with 2 equiv. of 2,6-di-*tert*-butyl-4-methylthiopyrylium cation (**62**) to yield the trimethine dye **225** presumably through the intermediacy of the anilino vinyl derivative **239** (81JAP81-30465). Analogous anilino vinyl derivatives (**240** and **241**) have been prepared by reaction of 4-methyl-2,6-diphenylthiopyrylium (**204**) and selenopyrylium (**205**) ions, respectively, with ethyl *N*-phenylformimidate ($\text{PhN}=\text{CHOEt}$) (74KGS53).

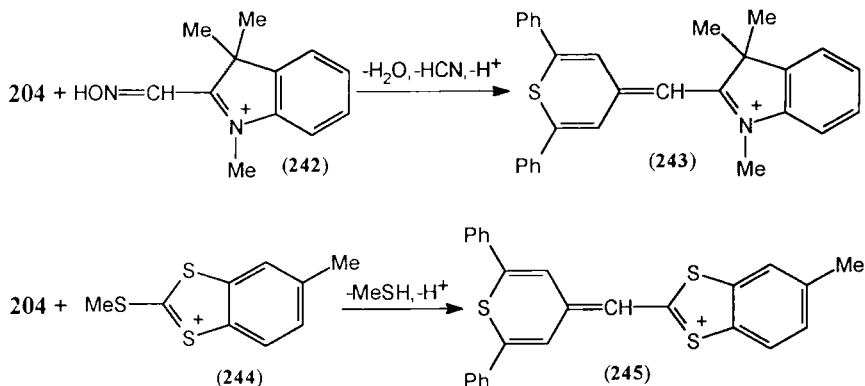


The condensation between α - or γ -alkylchalcogenopyrylium salts and orthoesters leads to trimethine dyes as shown in Eq. (7). The reaction is carried out in hot Ac_2O or AcOH or mixtures of the two solvents, in



the presence of a base such as pyridine or sodium acetate (56HCA217; 74KGS49; 84KGS451, 84KGS1486; 87KGS760). Alkoxyvinyl chalcogenopyrylium derivatives are formed as intermediates.

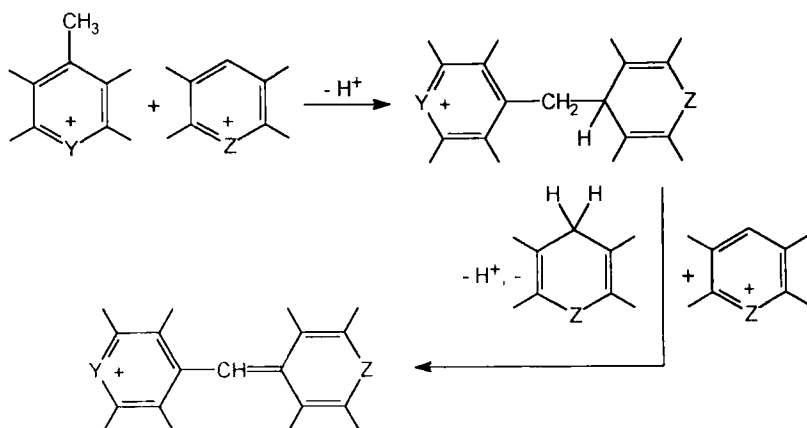
Cationic substrates with a leaving group can undergo the nucleophilic substitution by alkylidenechalcogenopyrans. Thus the indolium cation **242** reacts with 4-methyl-2,6-diphenylthiopyrylium ion (**204**) in Ac_2O in the presence of AcONa to yield the condensation product **243**; similarly 2-methylthio-5-methyl-1,3-benzodithiolylium (**244**) undergoes the nucleophilic substitution by **204** in AcOH with AcONa to yield compound **245** (66HCA2046). Analogous substitutions occurs with alkylthiochalcogenopyrylium ions yielding monomethine cyanine dyes (75KGS612; 80KGS898; 81JAP81-14560; 85MI3; 88KGS167). For example the symmetrical monomethine dye **30** can be prepared by reaction of 2,4-di-*tert*-butyl-6-methylthiopyrylium (**110**) and 2,4-di-*tert*-butyl-6-ethylthiopyrylium (**160**) (88KGS167).



Similar substitutions can also occur with hydrogen as leaving group if a suitable oxidant is present; this usually is the cationic substrate itself (Scheme 14). The products are also in this case monomethine cyanine dyes (66HCA2046; 73KGS1004; 74KGS49).

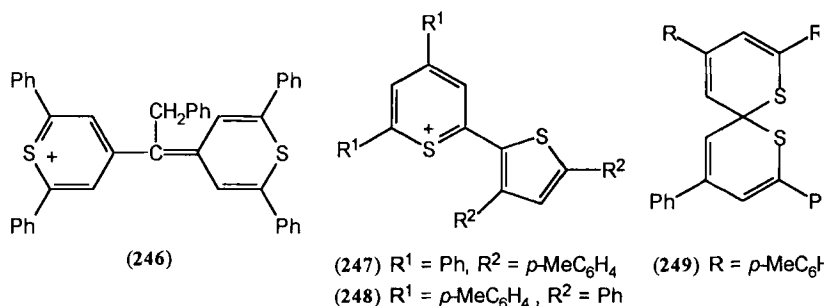
A variant of this reaction is illustrated by the reaction of 2,6-diphenylthiopyrylium (**18**) and 2,6-diphenyl-4-stiarylthiopyrylium in the presence of NaOAc in Ac_2O or CHCl_3 , yielding the benzylmethine cyanine dye **246** (77URP546615). In this case the hydride transfer is probably intramolecular.

An interesting reaction has been reported to occur between 4,6-diaryl-2-methylthiopyrylium salts and 3,5-diaryl-1,2-dithiolylium salts in boiling acetic acid and pyridine [77JCS(P1)1511]. If the aryl groups present in one of the two heterocycles are different from those present in the other,

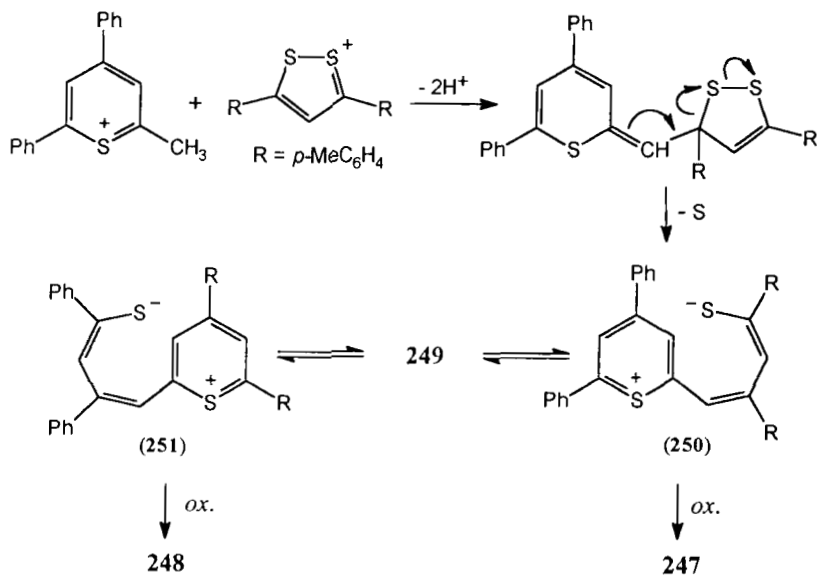


SCHEME 14

e.g., phenyl groups in the thiopyrylium ring and tolyl groups in the dithiolylium ring or vice versa, the product consists in a mixture of two isomeric thienylthiopyrylium ions **247** and **248** in which the aryl substituents are scrambled. This results points clearly to a reaction intermediate, such as the spirobithiopyran **249**, in which the aryl substituents originally present in the dithiolylium salt have become equivalent, in their site occupancy, to those originally present in the thiopyrylium salt. The proposed reaction mechanism is reported in Scheme 15. The products are formed by oxidation of intermediates **250** and **251** which are in rapid equilibrium between them through the spirobithiopyran **249**. It is not clear whether the oxidizing agent is extruded sulfur or atmospheric oxygen.

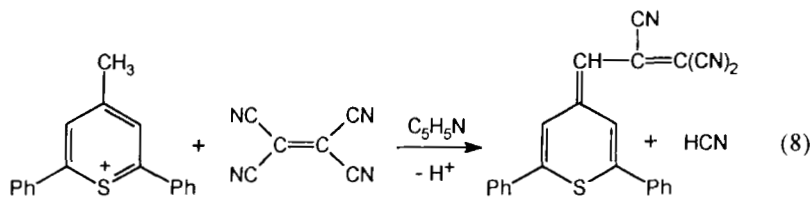


Reaction of 2,6-diphenyl-4-methylthiopyrylium (**204**), and 4,6-diphenyl-2-methylthiopyrylium (**109**) salts with tetracyanoethylene in pyridine gives tricyanopropenylidene thiopyrans as shown in Eq. (8). Two alternative reaction mechanisms have been proposed (77JHC1245). If the reaction is carried out in methanol in the absence of pyridine only charge-transfer

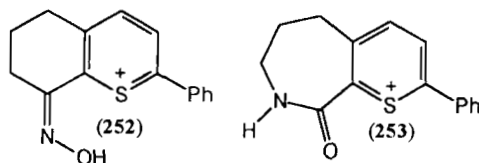


SCHEME 15

complexes between the anhydrobases and tetracyanoethylene are observed in solution.



Nitrosation of tetrahydrothiocromenylium ions [**77** $R^1 = \text{Ph}$, $p\text{-MeOC}_6\text{H}_4$, $R^2 = \text{H}$, Ph , $p\text{-MeOC}_6\text{H}_4$; $n = 2$], or octahydrothio- (**79**, $R = \text{H}$, $n = 2$) and -selenoxanthylum ions, with sodium nitrite in AcOH containing EtOH and Ac_2O affords a nitroso derivative, which rearranges immediately to furnish a tautomeric oxime in the *Z* configuration; e.g., **77** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, $n = 2$) is converted into the *Z*-oxime **252** (85ZOR2617; 89ZOR2246; 90ZOR405). The oxime **252** underwent Beckmann rearrangement to give the lactam **253** in good yield (89ZOR2246).

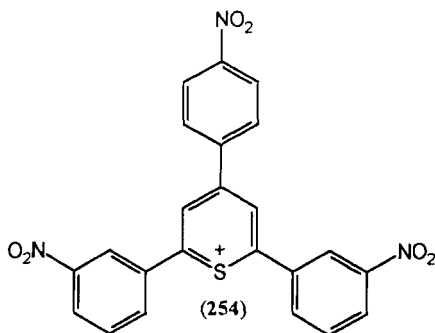


2,6-Diphenyl-4-methylthiopyrylium (**204**) and 4,6-diphenyl-2-methylthiopyrylium (**109**) ions have been brominated in AcOH containing $\text{Hg}(\text{OAc})_2$ affording the corresponding thiopyrylium ions in which the methyl group is converted into the dibromomethyl group (77URP546614).

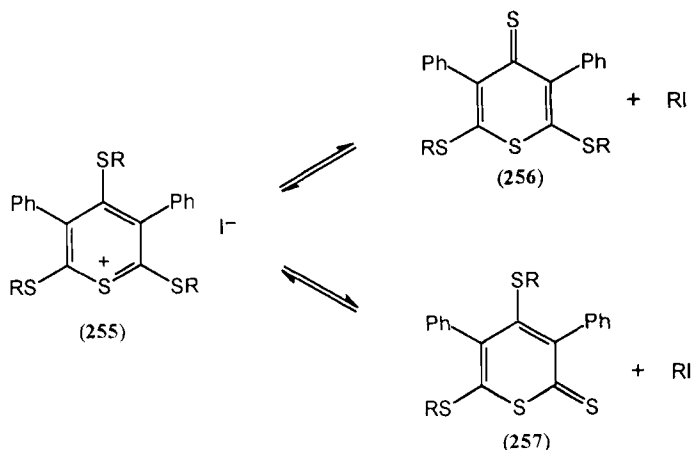
2. Reactions of Other Substituents

There are only scattered examples about reactions of substituents other than alkyl groups.

Because of the deactivating effect of the positive charge, no electrophilic substitution is known for the chalcogenopyrylium rings; however, aryl substituents may be substituted electrophilically. Thus the phenyl ring of 2,6-di-*tert*-butyl-4-phenylthiopyrylium ion (**46**) has been nitrated by 100% HNO_3 to yield the product of *para*-substitution **43** (86JA3409). Nitration of 2,4,6-triphenylthiopyrylium cation (**9**) has been reported to give the trinitroderivative **254** (83MI1). An independent attempt to nitrate cation **9** with 100% HNO_3 afforded a yellow solid that was not characterized because of rapid decomposure by contact with air (85UPI).



Alkylthiopyrylium salts can be dealkylated by various nucleophilic reagents to give thiopyranthiones. Thus cations **255** ($\text{R} = \text{Me}, \text{Et}$) can be dealkylated by iodide ion after heating at 100°C in bromobenzene giving mixtures of thiopyran-2- and 4-thiones (67JOC3144); 2,4-dimethylthiopyrylium ion is demethylated in refluxing pyridine to yield only the corresponding thiopyran-2-thione (81TL4507). Small amounts of alkyl iodides catalyze the rearrangement of 4*H*-thiopyran-4-thiones of the type **256** into their 2*H* isomers **257**. The reaction proceeds through the alkylation of **256** to yield the thiopyrylium salt **255**, which is then dealkylated at the 2-position by iodide ion to yield **257** (67JOC3144). By heating the iodide of cation **255** ($\text{R} = \text{Et}$) in acetonitrile, the 4-ethylthio group is converted into a methylthio group. This unusual exchange reaction, which does not

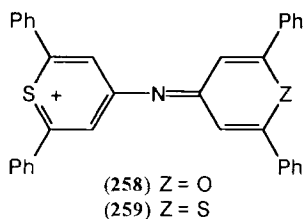


occur with BF_4^- as counter-ion has not been well understood (67JOC3144). 2,6-Dimethyl-4-methylthiopyrylium (**161**) is demethylated by NaHS in water to give the corresponding thiopyran-4-thione [56AC(R)821]. It is probable, however, that in this case the nucleophilic attack occurs at the C-4 ring atom and not at the methyl group (Section IV,C,4).

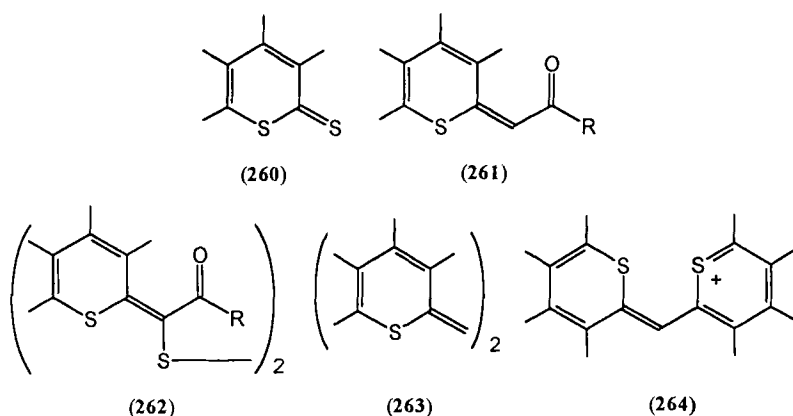
4-Ethoxy-2,6-diphenyltelluropirylium underwent dealkylation, instead of the expected substitution of the alkoxy group, by reaction with diethylamine in ethanol to yield the corresponding telluropyrone-4-one [**140**, Z = Te, R = Ph] (82JOC5235).

3-Acetoxythiopyrylium salts **195** and **196** have been deacetylated by treatment with trifluoroacetic acid to yield cations **194** and **107**, respectively [75JCS(P)2099].

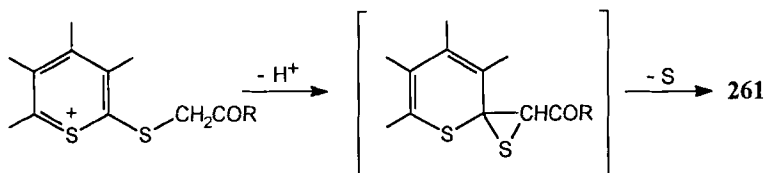
4-Amino-2,6-diphenylthiopyrylium salt (**157**) reacts with 4-methoxy-2,6-diphenylpyrylium or thiopyrylium (**143**) in acetonitrile in the presence of a nonnucleophilic amine (EtNPr'_2) to yield the azacyanine dyes **258** or **259** (77JHC539).



2-Acylmethylthiopyrylium salts (**163**), in polar solvents such as ethanol, dimethylformamide, pyridine, acetic acid, undergo transformations that lead to one or several of the compounds **260–264**. From salts of the



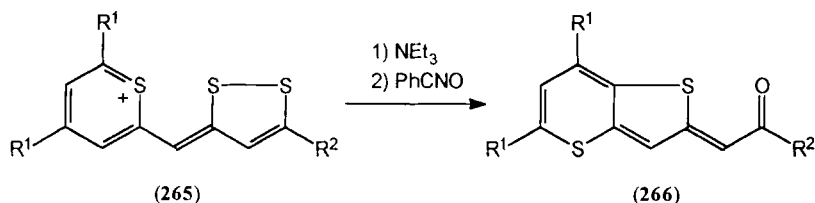
type **163** with alkyl groups in the β positions, under all conditions except in boiling acetic acid, the thiopyranylidene ketone **261** is the main product. It is always accompanied by the corresponding thiopyran-2-thione **260**. With salts of the type **163** with $R = \text{Me}$, and aryl groups in the 4,6 positions, at room temperature, the disulfide **262** is generally obtained. In boiling ethanol or acetic acid, compound **264** is formed, but in boiling dimethylformamide the reaction gives the thiopyranylidene ketone **261**. Boiling in dimethylformamide is, in fact, a convenient method to reduce the disulfide **262** to the corresponding thiopyranylidene ketone **261**. With salts of the type **163** with $R = \text{Ph}$, and aryl groups in the 4,6 positions, the thiopyranylidene ketone is always obtained together with various quantities of **260**, **262**, and **263**, the best results being observed with boiling pyridine or dimethylformamide. In boiling acetic acid all the studied salts give the monomethine dye **264** [80BSF(2)427]. The proposed mechanism for the formation of thiopyranylidene ketone **261** is reported in Scheme 16. The key intermediate is a thiirane derivative that splits off a sulfur atom to yield the product. A mechanism for the formation of the monomethine dye **264** has been also proposed; the key step would be the reaction of a molecule of thiopyranylidene ketone **261**, formed in the reaction medium, with a molecule of substrate [80BSF(2)434].



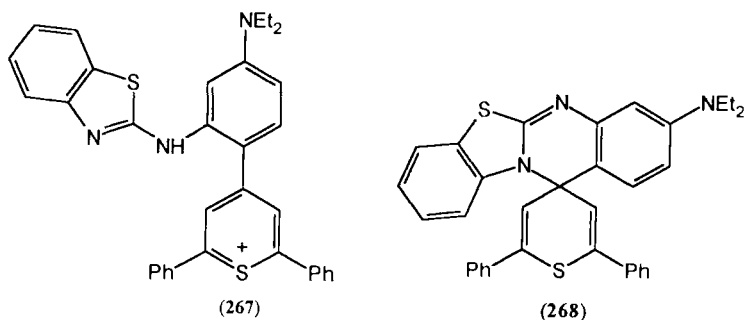
SCHEME 16

The thermal decomposition of 2-acylmethylthiopyrylium salts to yield thiopyranylidene ketones has been exploited by other authors as well (74BSF1356; 84AP938; 86MI3; 87FES465).

Cations of the type **265**, possessing both a thiopyrylium and a dithiole ring, when treated with triethylamine lead to unstable neutral compounds. However, if the reaction is followed by the addition of benzohydroxymoyl chloride [PhC(=NOH)Cl], which *in situ* generates benzonitrile *N*-oxide, compounds of the type **266** are obtained. A mechanism has been suggested for such transformation [80BSF(2)577].



The colored thiopyrylium cation **267** is deprotonated to yield the colorless spiro-4*H*-thiopyran **268** (83HCA2165). Investigation of the halochromic properties of **267** has been carried out in MeOH/H₂O solutions.



C. REACTIONS INVOLVING RING ATOMS

1. Reductions

Reductions of chalcogenopyrylium ions that are not the result of a nucleophilic attack, such as one-electron reductions and hydrogenation reactions, are discussed in this section.

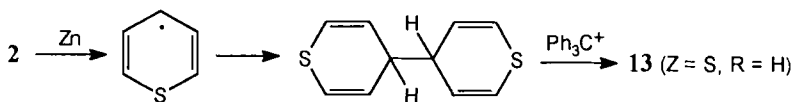
Chalcogenopyrylium ions can undergo one-electron reduction when treated with zinc powder in a degassed aprotic solvent. The product is a neutral chalcogenopyranyl radical, which in some cases is stable enough

to be studied by spectroscopic techniques, such as UV and ESR (67MI3; 70MP613; 72CC60; 86NJC345; 90KGS1480) (Section II,C,3). The factors affecting the stability of chalcogenopyranyl radicals, with particular regard to their tendency to dimerize, have been discussed in Section II,D.

Zinc reduction of chalcogenopyrylium ions has found application in synthesis. In order to prepare 4,4'-bithiopyrylium dication [**13** ($Z = S$, $R = H$)], thiopyrylium (**2**) is first reacted with excess zinc in acetonitrile at 0°C under a nitrogen atmosphere, and then with triphenylmethyl fluoroborate, iodide, or perchlorate to give the corresponding bithiopyrylium salt (71TL3999). According to the authors the reaction occurs as shown in Scheme 17.

Other authors showed that when the zinc reduction is carried out with 2,6-diarylthiopyrylium or selenopyrylium salts the product is the corresponding γ,γ' -bithio- or biseleno-pyranylidene **14** ($Z = S$, Se, $R = Ar$) [81TL2771; 84BSF(2)241; 85MI4]. According to Fabre *et al.*, the γ,γ' -bipyranil intermediate, as soon as it forms, undergoes hydride abstraction by the unreacted starting cation and then deprotonation to yield the corresponding bipyranilidene [76CR(C)175].

Besides zinc, a number of other species can behave as monoelectronic reducing agents of thiopyrylium ions. Thus the unsubstituted thiopyrylium (**2**) and 2,4,6-triphenylthiopyrylium (**9**) have been reduced by alkali metals, the reactivity order ($K > Na > Li$) being the reverse of that of the ionization energies (80MI6). Bis-(2,6-diphenylthiopyrylium-4-yl)-ethyne dication (**130**) has been reduced by a large excess of triethylamine to give the cumulene **73**; interestingly zinc reduction of **130** afforded only a minute amount of **73** (81CC1143). Triethylamine also converted 2,6-di-*tert*-butylthiopyrylium cation (**26**) to the corresponding bithiopyranilidene **14** ($Z = S$, $R = Bu^t$) (85T811). 2,4,6-Triphenylthiopyrylium cation (**9**) undergoes an electron-transfer reaction with isopropoxide or *tert*-butoxide anion but not with methoxide or ethoxide anion, the latter anions giving addition products (86ZC400). Thiopyranil radicals have been also produced by photoirradiation of thiopyrylium salts in tetrahydrofuran and/or 1,2-dimethoxyethane with or without added reducing agents (85BCJ2600; 89BCJ2279). In fact, whereas 2,4,6-triphenylthiopyranil radical (**51**) is formed by electron transfer from the solvent with relatively high quantum yields (85BCJ2600), pentaphenylthiopyranil radical (**54**) is formed by pho-



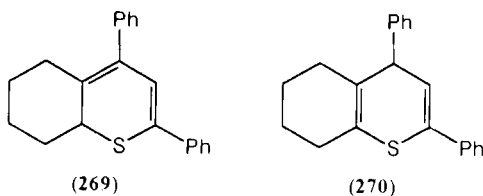
SCHEME 17

toirradiation only when a reductant, such as triphenylphosphine or hexamethylbenzene, is added to the solution (89BCJ2279).

Thiopyrylium and selenopyrylium cations possessing a leaving group can undergo a reductive dimerization with a number of reagents. Thus 4-chloro-2,6-dimethylthiopyrylium (**148**) by treatment with MnSe_2 gives bithiopyranylidene **14** ($Z = \text{S}$, $R = \text{MeS}$) [84BSF(2)241]. Similarly 4-chloro-2,6-diphenylselenopyrylium (**150**) reacts with zinc or TiCl_3 to yield the corresponding biselenopyranylidene **14** ($Z = \text{Se}$, $R = \text{Ph}$) [84BSF(2)241].

Thiopyrylium salts can be reduced to the corresponding thiacyclohexanes by catalytic hydrogenation. Thus the hydrogenation of cations **9**, **18**, **77** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, Ph , $n = 2$), **79** ($R = \text{H}$, Me , $n = 2$), and **204** has been studied with various catalysts (Pd/C , Rh/C , PdS/C , $\text{PdS/Al}_2\text{O}_3$, PtO_2) under a variety of conditions. The catalyst formed by 10% Pd/C appears to be the most convenient; best reaction conditions are 80–100°C and 80–100 atm (82MI7, 82ZOR2435). The hydrogenation of type **77** cations ($R^1, R^2 = \text{H}$, Ar) over Pd/C at 50 or 100 atm gave *cis*-1-thiadecalins with R^1 and R^2 in the equatorial orientation (87KGS614). The hydrogenation of octahydrothioxanthylum ions [**79** ($R = \text{H}$, Me , Ph , $n = 2$)] over Pd/C is stereoselective and gives 65–86% of the corresponding *cis,syn,cis*-perhydrothioxanthenes (87KGS1187).

Thiopyrylium salts can be also reduced by zinc in hydrochloric acid. Thus cation **77** ($R^1 = R^2 = \text{Ph}$, $n = 2$) by treatment with Zn/HCl gave a mixture of 6*H*-thiopyran **269**, 4*H*-thiopyran **270**, and the corresponding thiadecaline [71KGS(S)85].



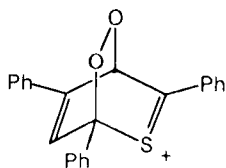
2. Oxidations

Only a few oxidation reactions have been reported for chalcogenopyrylium salts. Manganese dioxide oxidizes thiopyrylium (**2**) in chloroform to 2-thiophenecarboxaldehyde in 71% yield (67G397). In contrast 5-acetyl-2-(*p*-methoxyphenyl)thiopyrylium ion (**57**) is oxidized by MnO_2 in CHCl_3 to produce the corresponding thiopyran-2-one in only 5% yield [73AC(R)563; 75T3059]. The same substrate is also oxidized by sulfur in pyridine to give the corresponding thiopyran-2-thione, but always in very

low yield [73AC(R)563; 75T3059]. Manganese dioxide in acetonitrile has been used to oxidize 2,6-diphenylselenopyrylium cation (**19**) to the corresponding selenopyran-4-one [**140** ($Z = \text{Se}$, $R = \text{Ph}$)] (74KGS274).

Thiopyrylocyanine **11** ($Z = Y = \text{S}$, $n = 0$) undergoes one-electron oxidation with lead dioxide; the resulting dication radical, by loss of the central methinic proton, is converted into a cation radical, which has been studied by ESR (90KGS1480).

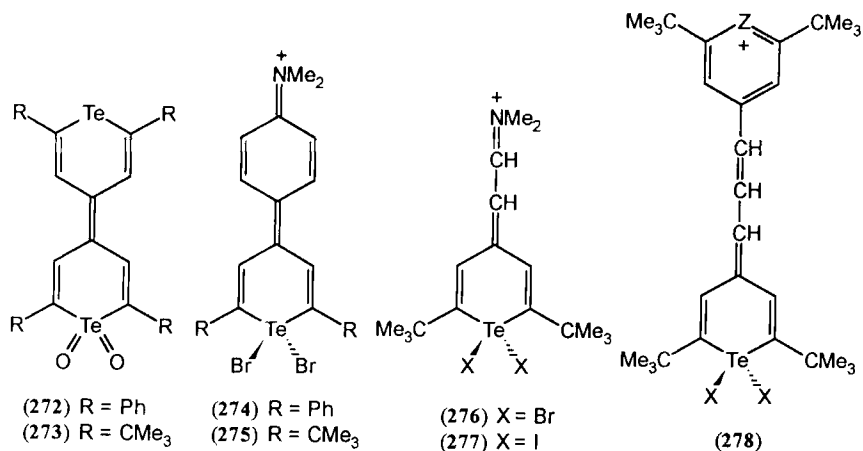
2,4,6-Triphenylthiopyrylium cation (**9**), when irradiated with UV light in methanol under an oxygen atmosphere, yields benzaldehyde, methyl benzoate, benzoic acid, and trace amounts of thiophenol (71TL4259). The reaction occurs between **9** in the excited triplet state and oxygen in the ground state. The peroxide **271** has been proposed as reaction intermediate.



(271)

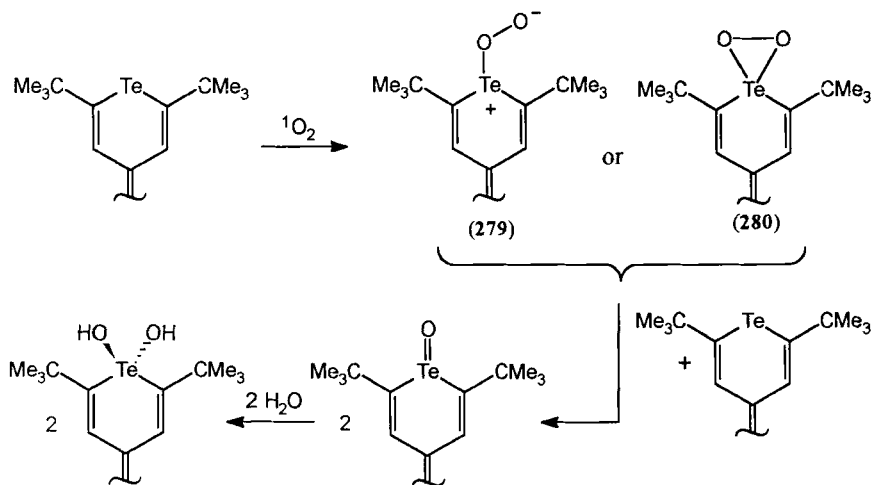
2,6-Disubstituted telluropyrilium cations **20** and **28** in pyridine with triphenylphosphine under aerobic conditions gave an oxidative dimerization to produce 1,1-dioxo(telluropyranylidene)telluropyrans **272** and **273**, respectively (87JOC2123). The reaction is also successful with the exclusion of oxygen if triphenylphosphine oxide is substituted for triphenylphosphine. The oxidative dimerization could not be extended to thiopyrylium cation **26** and selenopyrylium cation **27**, which gave the corresponding bipyranylidenes **14** ($Z = \text{S}$, Se , $R = \text{Bu}^t$).

Telluropyrilium salts undergo oxidative addition of a halogen molecule across the tellurium atom (86MI2). Thus addition of bromine to cations **68** and **70** yields cations **274** and **275**, respectively. Cations **276**, **277**, **11** ($Z = \text{Te}$, $Y = \text{TeCl}_2$, TeBr_2 , TeI_2 , $n = 0$) and, **278** ($Z = \text{Te}$, Se , $X = \text{Br}$) have been similarly prepared. The oxidative addition of halogens removes the Te orbitals capable of π -bonding to the carbon π -framework. Ultraviolet spectra of the dihalide complexes suggest that the strength of the $\text{Te}-\text{X}$ bonds follows the order $\text{Cl} > \text{Br} \gg \text{I}$. In solution, the diiodides apparently are not stable, since the observed absorption spectra of the diiodides appear to be those of the parent telluropyrilium dyes. The dihalide complexes are easily reduced, regenerating the starting telluropyrilium dyes and two equiv. of halide, as shown by cyclic voltammetry. Chemical reduction of cations **278** ($Z = \text{O}$, S , Se , $X = \text{Br}$) has been



carried out with sodium bisulfite (90JMC1108, 90USP4963669). Interestingly, cation **278** ($Z = \text{Te}$, $X = \text{Br}$) was observed to have fluxional ^1H NMR behavior. The two Te atoms become equivalent by some temperature-dependent exchange process of bromide ligands. The exchange was first-order with respect to the dye in CD_3CN and second-order in $\text{CDCl}_2\text{CDCl}_2$. In CDCl_3 the exchange was a mixture of first- and second-order processes.

Singlet oxygen is efficiently produced on irradiation of air-saturated methanolic solutions of telluropyrrolyl trimethine dyes **229–232** (88JA5920; 90JA3845). It rapidly reacts with telluropyrrolyl dyes in the presence of water to yield products derived from formal oxidative addition of hydrogen peroxide across tellurium, i.e., **278** ($Z = \text{O}$, S , Se , Te , $X = \text{OH}$). Compounds of the type **278** with $X = \text{OH}$ are found to be dibasic acids, to exchange hydroxyl ligands with tellurium(II) centers, to undergo thermal reductive loss of hydrogen peroxide, and to transfer intramolecularly oxygen from tellurium(IV) to an adjacent carbon center (91MI3). Addition of hydrogen peroxide to telluropyrrolyl dyes **229–232** leads to the same addition products **278** but is ca. 8 order of magnitude slower, whereas the reaction with superoxide radical anion leads to products other than **278**. Thus the mechanism reported in Scheme 18 has been proposed for the oxidation of telluropyrrolyl dyes **229–232**. The initial step is thought to be the formation of either a pertelluroxide (**279**) or a telluradioxirane (**280**) intermediate. The behavior of chalcogenopyrrolyl dyes **223–228** has been also investigated with respect to their abilities to generate singlet oxygen and to react with singlet oxygen. The production of singlet oxygen is due to the reaction of the triplet state of the dye with ground-state oxygen via a spin-allowed process. As the heteroatoms become heavier, spin-orbit coupling increases, producing higher triplet yields. Triplet yields increase



SCHEME 18

from 0.0004 for **223** to 0.18 for **232**, whereas quantum yields for singlet oxygen production increase from 0.0004 for **223** to 0.12 for **232**. All the chalcogenopyrylium dyes **223–232** react with singlet oxygen; however, the oxidation products have been characterized only for the tellurium-containing dyes. Whereas pyrylium dyes should be attacked only at the hydrocarbon framework, sulfur- and selenium-containing dyes could be attacked both at the heteroatom and at the carbon framework. The higher reactivity of the tellurium-containing dyes appears to reflect reaction at the tellurium atom. Evidences have been put forward indicating that quenching of singlet oxygen by chalcogenopyrylium dyes **223–232** follows the Corey–Kahn mechanism (92MI4). This mechanism assumes that the heavy atoms are good nucleophiles for electrophilic singlet oxygen, perhaps leading to unstable oxidative addition products, and that the magnitude of spin–orbit coupling is directly related to the heavy-atom effect on quenching constants (87SCI68; 90TL1389). Interestingly there is a linear free-energy relationship between the reactivity of chalcogenopyrylium dyes **223–232** with singlet oxygen and with hydrogen peroxide, the latter reagent being less reactive and more selective than the former (92MI4).

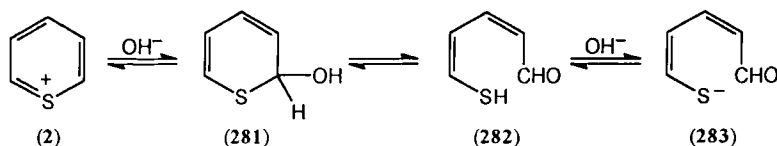
Two catalytic reactions of cation **232** have been described in which the dihydroxytellurium species **278** ($Z = \text{Te}$, $X = \text{OH}$) is produced as an intermediate (90JA4086; 92MI1, 92MI5). In one reaction, the telluropyrylium dye **232** is oxidized to **278** via irradiation of air-saturated aqueous solutions. Thermal reductive elimination of hydrogen peroxide regenerates the starting telluropyrylium dye, allowing the net photochemical conversion of oxygen and water to hydrogen peroxide. In a second reaction, the

formation of **278**, via reaction of a catalytic amount of telluropyrpylium dye **232** with either singlet oxygen and water or with hydrogen peroxide, leads to the oxidation of certain leucodyes and thiophenol, showing that **278** is an efficient two-electron oxidizing agent that can be used as catalyst to accelerate reactions using hydrogen peroxide as two-electron oxidizing agent. In both of these systems, a Te(II)–Te(IV)–Te(II) cycle avoids the use of a sacrificial electron donor. Neither seleno- nor thio-pyrpylium dyes **227** and **228** show analogous catalytic efficiencies.

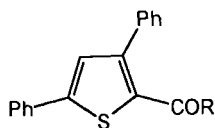
Seleno- and telluro-containing chalcogenopyrpylium dyes can be promising, as singlet-oxygen-producing photosensitizers, in photodynamic therapy (Section V).

3. Reactions with Oxygen Nucleophiles

The hydrolysis of the unsubstituted thiopyrpylium cation (**2**) has been studied in water at various pH values (65MI3; 67G397). Cation **2** is stable in aqueous solutions up to pH 6. In the range $6 < \text{pH} < 11$ the cation coexists with thioglutaconic aldehyde (**282**) and its conjugated base **283**. Although the presence of the pseudobase **281** could not be evidenced by UV spectra because of superimposition of absorption bands, it cannot be excluded. At $\text{pH} \geq 11$, **283** is the only species present in solution as confirmed by UV and ^1H NMR. The reaction is fully reversible in that treatment with acids regenerates cation **2**. The presence of species **282** and **283** at equilibrium casts some doubts (65MI4; 67G397) on the significance of the pK_{R^+} value of cation **2** (8.7) determined by potentiometric methods (64JA5630).



Interestingly, species of the type **283**, which can be also obtained by reaction of pyrpylium salts with sulfide anion (Section III,B,1), are easily oxidized to yield 2-acylthiophenes. Thus 2-benzoyl-3,5-diphenylthiophene (**284**) can be obtained either by boiling 2,4,6-triphenylthiopyrpylium ion (**9**) in wet pyridine saturated with sulfur [77JCS(P1)1511] or by reaction of 2,4,6-triphenylpyrpylium (**8**) with sodium sulfide in acetone followed by oxidation with air or iodine [75ACS(B)791]. Analogously, 2-formyl-3,5-diphenylthiophene (**285**) has been obtained on treatment of 2,4-diphenylthiopyrpylium (**154**) with iodine and aqueous sodium carbonate in acetonitrile (84JOC2676). The 2,5-linkage by sulfur has a par-

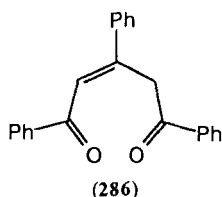


(284) R = Ph

(285) R = H

allel reaction in the oxidation of thiopyrylium (**2**) by manganese dioxide to 2-thiophenecarboxaldehyde (Section IV,C,2).

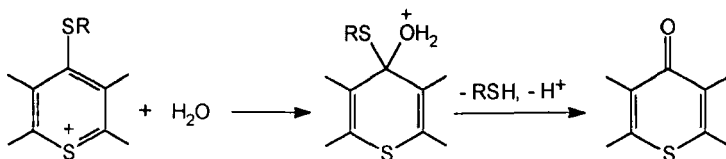
Reaction of 2,4,6-triphenylthiopyrylium ion (**9**) in wet pyridine at room temperature [75ACS(B)791] or with triethylamine in CHCl_3 followed by water addition (85T811) affords the 1,5-enedione **286**, which is the product of hydrolysis of the keto-thioenol formed on ring-opening of the pseudobase of **9**.



(286)

If a leaving group is present in the α or γ position of a thiopyrylium salt, the reaction with water leads to a thiopyranone, via a nucleophilic substitution of the $\text{S}_{\text{N}}\text{Ar}$ type. Thus a number of thiopyran-2- and 4-ones have been prepared by boiling the corresponding alkylthiopyrylium salts in water-organic solvents mixtures (Scheme 19) [65LA188; 73AC(R)563; 74BSF1356; 76BSF1195; 81JAP81-14560, 81JAP81-14561, 81JAP81-29586, 81JAP81-30465]. An attempt to prepare 2,6-dimethylthiopyran-4-one by treatment of 2,6-dimethyl-4-methylthiopyrylium ion (**161**) with potassium hydroxide in methanol led to unpurifiable resinous products (60BCJ1467).

With chlorine or bromine as leaving group, the reaction with water is not clean, giving thiopyranones, thiopyranthiones, and ring-opening products (69JPR61). Halogenothiopyrylium salts can be conveniently con-

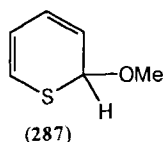


SCHEME 19

verted into thiopyranones by refluxing them in acetic acid and butylamine or benzylamine, to yield an acetoxythiopyrylium salt, which is then hydrolyzed in water [69JPR61; 79JCS(P1)1957].

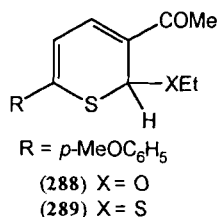
The reaction of halogenothiopyrylium salts with oxygen nucleophiles other than water occurs according to the S_NAr mechanism yielding the corresponding O-substituted thiopyrylium salts. Thus 4-chloro-2,6-diphenylthiopyrylium ion (**149**) reacts with the conjugate base of alcohols, phenols, and organic acids to yield the corresponding substitution products (71M11). Analogously, 4-chlorothiopyrylium perchlorate reacts with sodium phenoxide and sodium methoxide to yield 4-phenoxy- and 4-methoxy-thiopyrylium salts, respectively (75T2669).

The reaction of alkoxyde anions with thiopyrylium salts devoid of a leaving group leads to the formation of stable *2H* and/or *4H* adducts. Thus thiopyrylium (**2**) iodide reacts with a methanol solution made alkaline by sodium hydrogen carbonate to yield 2-methoxy-*2H*-thiopyran (**287**) (65M13; 67G397). Treatment with acids regenerates the starting cation, showing that the reaction is reversible. Analogously, 2,4,6-triarylthiopyrylium salts react with sodium methoxide in methanol to yield the corresponding *2H* adducts (80JOC5160; 83ZC333; 86JPR373), whereas, in acetonitrile, the reaction of 2,4,6-triphenylthiopyrylium cation (**9**) with methoxide ion leads to the competitive formation of both the *2H* and the *4H* adducts (80JOC5160). This seemingly different behavior depends only on the fact that the equilibration between the adducts is very slow in acetonitrile; i.e., the reaction is under kinetic control in acetonitrile and under thermodynamic control in methanol. In fact, a kinetic study of the reaction in methanol by stopped-flow technique has evidenced the fast formation of both adducts followed by the conversion of the *4H* adduct into the more stable *2H* isomer (82JOC960).



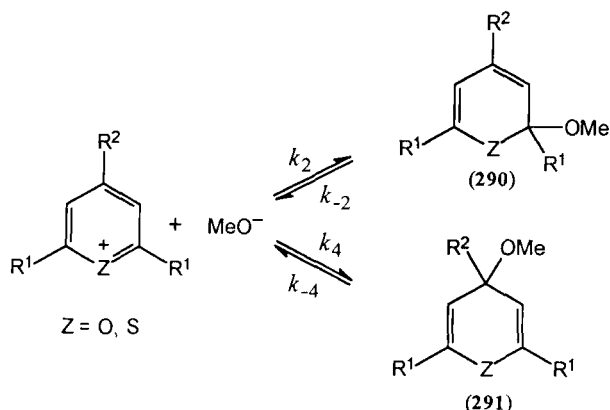
The behavior of 2-methoxy-*2H*-thiopyrans, formed on addition of methoxide anion to 2,4,6-triarylthiopyrylium cations, toward some nucleophiles and electrophiles was investigated (83ZC333; 86JPR373). The results are easily accounted for by considering the methoxy-adducts in equilibrium with the parent ions.

5-Acetyl-2-(*p*-methoxyphenyl)thiopyrylium cation (**58**) when refluxed in a mixture of ethanol and benzene 1 : 5 yields the *2H* adduct **288** (75T3059).



Whereas 2,4,6-triphenylthiopyrylium cation (**9**) reacts with methoxide or ethoxide anion to give the corresponding *2H* adduct, it undergoes an electron transfer with isopropoxide or *tert*-butoxide anion to yield the neutral radical **51** (86ZC400).

Rates and equilibria for the reaction of a number of pyrylium and thiopyrylium cations symmetrically substituted in the 2,6-positions with methoxide ion in methanol have been studied in great detail by Doddi and Ercolani. Besides providing quantitative data about the effects of the ring-heteroatom and of substituents in pyrylium and thiopyrylium ions, these studies were aimed at gaining a deeper understanding of cation-anion combination reactions. A first study, regarding the reaction of pyrylium and thiopyrylium salts with various α -substituents (Ph or Bu') and γ -substituents (H, Me, Bu', Et₃C, or MeO), was carried out by ¹H NMR at -40 and 25°C [86JCS(P2)271]. The reaction consists in two reversible and competitive processes relative to the formation of *2H* and *4H* adducts, respectively (Scheme 20). At -40°C the reaction is under kinetic control; therefore the ratio of the concentration of the adducts coincides with the ratio of the corresponding kinetic constants ($[\mathbf{291}]/[\mathbf{290}] = k_4/k_2$). At 25°C, since the reaction is under thermodynamic control, the ratio of the concentration of the adducts coincides with the ratio of the corresponding equilibrium constants ($[\mathbf{291}]/[\mathbf{290}] = K_4/K_2$). From the obtained data the following conclusion have been drawn: (a) both the kinetic regioselectivity, measured by the ratio k_4/k_2 , and the thermodynamic regioselectivity, measured by the ratio K_4/K_2 , are always higher for thiopyrylium ions than for the corresponding pyrylium ions; (b) in most of the cases the *4H* adduct is the principal product of kinetic control ($k_4/k_2 > 1$), whereas the *2H* adduct is the principal product of thermodynamic control ($K_4/K_2 < 1$); (c) the nucleophilic attack shows a certain sensitivity to steric effects. A detailed kinetic and thermodynamic study of the methoxide addition to the 2,6-di-*tert*-butyl-4-aryl-thiopyrylium cations **43–49** and to the corresponding pyrylium cations **36–42** has been successively carried out (86JA3409, 86JOC4385). The observed kinetic patterns have confirmed that the rate-determining step is the combination of the nucleophile with the cations to give the adducts according to Scheme 20 and have disproved



SCHEME 20

the views indicating the ion pair formation as the rate-determining step in anion-cation combination reactions. Moreover, these studies have allowed the evaluation of the individual values of the kinetic and equilibrium constants. From these values it has been concluded that (a) pyrylium ions are more reactive than the corresponding thiopyrylium ions from both a kinetic and a thermodynamic point of view and (b) pyrylium ions show a greater sensitivity toward the electronic effects of substituents regarding both the kinetic and the equilibrium constants. Both these observations find justification in the higher carbocationic character of the pyrylium ring, which in turn is due to the higher electronegativity of oxygen. The fact that the kinetically favored product is not that thermodynamically more stable indicates that the transition states are significantly different from the final products. The variation of the kinetic regioselectivity in going from pyrylium to thiopyrylium is consistent with the charge distribution in the two cations reported in Section II,A, Fig. 1, indicating that the rates of nucleophilic attack are dominated by coulombic interactions. Since ^{13}C chemical shift is one of the best physical parameters to probe charge density, a correlation of the α and γ carbon shifts of the series 36–42 and 43–49 with the kinetic constants k_2 and k_4 , respectively, was attempted (88G291). However, the success was only partial. In both series there is a good correlation between the chemical shifts of α carbons and the corresponding $\log k_2$ values. In contrast, since the γ carbon shifts appear to be dominated by π -polarization effects (electron-withdrawing substituents have a shielding effect), they do not follow the trend of k_4 constants. The thermodynamic regioselectivity depends on the relative stability of the adducts; it has been evidenced by MNDO and AM1 calculations that 2-methoxy-2H-pyrans are much more stable than the

corresponding 4*H* isomers because of the anomeric effect between the geminal oxygen atoms (92JOC4431). This effect is less important in 2-methoxy-2*H*-thiopyrans and would explain the variation of the thermodynamic regioselectivity in going from pyrylium to thiopyrylium cations.

A kinetic study of the methoxide addition to a series of thiopyrylium ions and to the corresponding series of pyrylium ions has shown an interesting effect regarding how the α -substituents affect the kinetic constant k_4 [89JCS(P2)1393]. It has been observed that the effect of phenyl and *tert*-butyl groups as α -substituents follows a different order in the two series; i.e., the *tert*-butyl group is more activating than the phenyl group in the pyrylium series, but less activating in the thiopyrylium series. This effect has been tentatively explained by considering the superimposition of two factors, i.e., the different electronic effect of the two groups as measured by σ_p^+ and the steric inhibition of solvation of the ring heteroatom by the adjacent *tert*-butyl groups, the latter effect being more important in the pyrylium series. In the same paper it was also shown that steric effects on nucleophilic attack are analogous in the two series. The sensitivity to steric effects, which has been evaluated in the pyrylium series, is rather low ($\delta \sim 0.5$) (88JOC1729). The equilibrium constants are not affected by the steric hindrance of substituents unless these are very encumbering as the Et₃C group.

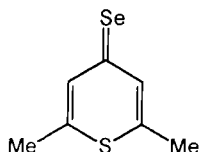
The equilibrium constants for the reaction of thiopyrylium ions with methoxide ion have also been utilized to evaluate *ipso*-substituent effects. In particular our estimate of the *gem*-dimethoxy effect (12 kJ mol⁻¹), i.e., the stabilizing interaction that occurs between two geminal methoxy groups, was in good accordance with a previous estimate based on data referring to the formation of negatively charged Meisenheimer adducts (82CRV77).

4. Reactions with Sulfur and Selenium Nucleophiles

The reactions of thiopyrylium ions with sulfur nucleophiles are analogous to those with oxygen nucleophiles. In the presence of a sufficiently good leaving group in the α or γ position, the reaction with hydrogen sulfide or with hydrosulfide anion leads to the formation of thiopyranthiones. Thus the 2-halogeno-substituted thiopyrylium cations **146** and **147** react with H₂S in benzene to yield the corresponding thiopyran-2-thione (69JPR61). The same transformation has been carried out with sulfur dissolved in pyridine (69JPR61).

2,6-Dimethyl-4-methoxy- and 2,6-dimethyl-4-methylthio-thiopyrylium (**161**) ions react with NaHS in water to give the corresponding thiopyran-

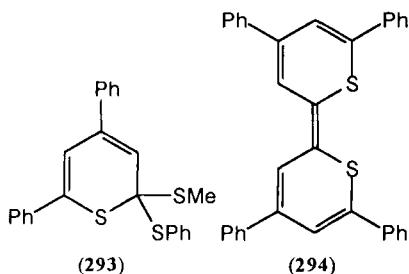
4-thiones [56AC(R)821; 58CB1224]. Analogously, cation **161** reacts with NaHSe to yield 2,6-dimethyl-4*H*-thiopyran-4-selone (**292**) (77CC177).



(292)

Thiols react with halogenothiopyrylium salts to give the product of substitution. Thus 4-chlorothiopyrylium reacts with thiophenol to give the 4-thiophenoxythiopyrylium ion (75T2669). The reactivity of 4-chlorothiopyrylium and *N*-methyl-4-chloropyridinium toward thiophenol has been compared by a competitive experiment. The thiopyrylium ion was demonstrated to be ca. 4 times more reactive than the pyridinium ion.

In the absence of a sufficiently good leaving group, stable adducts are formed. Thus 5-acetyl-2-(*p*-methoxyphenyl)thiopyrylium cation (**58**) reacts with ethanethiol in benzene to yield the 2*H* adduct **289** (75T3059). 2-Methylthio-4,6-diphenylthiopyrylium (**159**) ion reacts with sodium thiophenoxide to give the 2*H* adduct **293** (86S916). Heating of the adduct **293** yields the *Z*-2,2'-bithiopyranylidene **294** with a minor amount of the *E* isomer. Compound **294** can also be directly obtained by reaction of cation **159** with thiophenol and triethylamine.



(293)

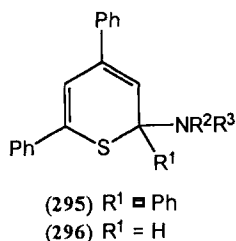
(294)

Some intramolecular additions to thiopyrylium ions involving sulfur as nucleophilic center have been reported in Sections IV,B,1 and 2.

5. Reactions with Nitrogen Nucleophiles

The reaction of thiopyrylium salts with amines can afford different products, depending on the substitution pattern of the heteroaromatic cation, the nature of the amine, and reaction conditions. In most cases

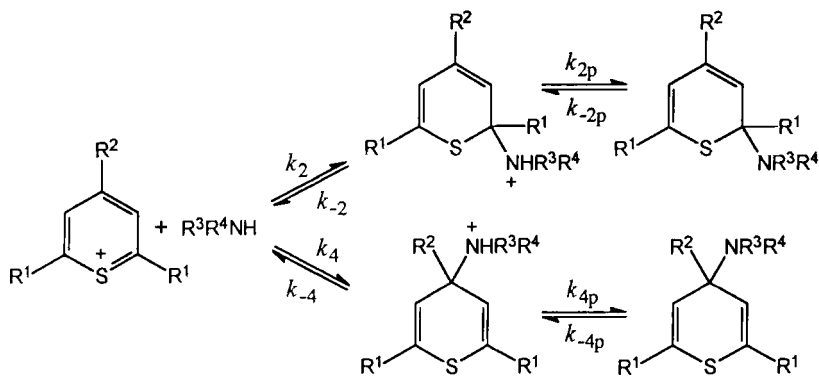
the primary interaction involves nucleophilic addition to the α and/or γ position of the thiopyrylium ring yielding thiopyran adducts, which in some cases can be isolated and/or characterized by spectroscopic methods. Thus 2,4,6-triphenylthiopyrylium ion (**9**) reacts with 2 equiv. of a primary or secondary amine in either Me_2SO or CH_3CN to yield the corresponding *2H* adduct **295**. Aniline yields the corresponding *2H* adduct only after the addition of 1 equiv. of triethylamine (82JOC3496). With primary amines the final products are 1-substituted pyridinium ions, which are formed from the corresponding *2H* adducts after several days at room temperature. Also, 2,4-diphenylthiopyrylium ion (**154**) reacts with butylamine or diethylamine in acetonitrile to yield the corresponding *2H* adduct **296**. The conversion of the butylamine adduct **296** into the corresponding *N*-butyl pyridinium ion is faster than that of the corresponding adduct **295**.



A number of 2,4,6-triarylthiopyrylium salts reacts with dialkylamines in diethyl ether to give stable crystalline 2-dialkylamino-*2H*-thiopyrans (83ZC144; 84EGP212964; 86JPR567). Reactions of these with a number of nucleophiles and electrophiles can be easily accounted for by considering them in equilibrium with the parent thiopyrylium ion and amine (86JPR567).

An example of intramolecular addition to a thiopyrylium ion involving nitrogen as nucleophilic center, i.e., the conversion of **267** to **268**, has been reported in Section IV.B.2.

A detailed kinetic and thermodynamic study of the reaction of 2,4,6-triphenylthiopyrylium cation (**9**) with butylamine, cyclohexylamine, piperidine, and morpholine has been carried out in dimethyl sulfoxide at 25°C (84JA7082, 84JOC1806). The reaction occurs according to Scheme 21. In all of the cases two kinetic processes have been observed, the first one involving the competitive formation of both the *2H*- and the *4H*-thiopyrans through the steady-state intermediacy of their corresponding charged adducts and the second one converting the *4H*-thiopyran into the thermodynamically more stable *2H*-thiopyran. The k_p and k_{-p} terms that appear in Scheme 21 refer to the proton transfer steps, involving the solvent and



SCHEME 21

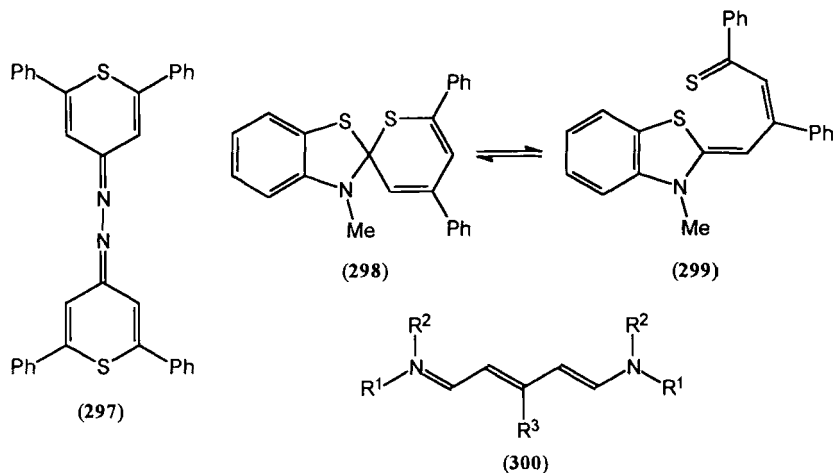
the amine in the forward reaction and their conjugate acids in the reverse reaction. The most interesting feature is that with primary amines the rate-controlling step is the nucleophilic attack, whereas with secondary ones the rate-controlling step is the deprotonation of the charged adducts. This behavior has been ascribed to the increasing steric hindrance in going from primary to secondary amines causing a decrease of the k_{2p} , k_{4p} constants and an increase of the k_{-2} , k_{-4} ones. The reaction of 2,6-di-*tert*-butyl-4-phenyl- (**46**) and 2,6-diphenyl-4-*tert*-butylthiopyrylium (**111**) ions with butylamine has also been investigated (89G205). The results indicate that, despite the increased hindrance on the reactions centers, obtained by replacing the phenyl group with the *tert*-butyl one, the rate-controlling step is always the nucleophilic attack to yield the charged thiopyrans, irrespective of the position (α or γ) that has undergone the $\text{Ph} \rightarrow \text{Bu}'$ substitution. The results also indicate a low sensitivity to steric effects at the electrophilic center, as observed in the reaction with methoxide anion (Section IV,C,3).

Thiopyrylium ions possessing a sufficiently good leaving group in α or γ position can undergo the nucleophilic substitution when treated with primary or secondary amines. Whereas secondary amines give aminothiopyrylium salts, primary amines yield products that can be formulated as either thiopyranimines or aminothiopyrylium salts, depending on the pH of the reaction medium. A number of substitution reactions on thiopyrylium salts have been reported in which a halogeno, an alkoxy, or an alkylthio group is replaced by an alkyl or aryl amine [69JPR61; 71KGS279; 72MI1; 73JPR679, 73URP382617; 75T2669; 76BSF1195; 77JCS(P1)1436, 77JCS(P1)1511] (see also the preparation of compounds **258** and **259** in Section IV,B,2). Phenylhydrazine and hydroxylamine behave as simple amines (65LA188; 69JPR61). Hydrazine, depending on the reaction condi-

tions, can react with one or both nitrogen atoms (69JPR61; 74LA1415). The second case is exemplified by the reaction of 4-methylthio-2,6-diphenylthiopyrylium ion (**162**) with hydrazine in dimethylformamide to yield the azine **297** (74LA1415).

The spiro[benzothiazoline-2,2'-(2*H*)-thiopyran] **298** has been prepared by reaction of 2-methylthio-4,6-diphenylthiopyrylium ion (**159**) and 2-methylaminobenzenethiol in ethanol [77JCS(P1)1511]. This product, which is probably formed via a nucleophilic substitution promoted by the nitrogen atom followed by nucleophilic attack of the sulfur atom, shows interesting behavior; it is a pale yellow solid at room temperature but becomes blue on being heated, gives a blue solution in ethanol, and forms a blue zone on chromatographic alumina. These color changes, which are similar to those occurring in spirobenzopyrans, may be attributed to the formation of the colored merocyanine tautomer **299**.

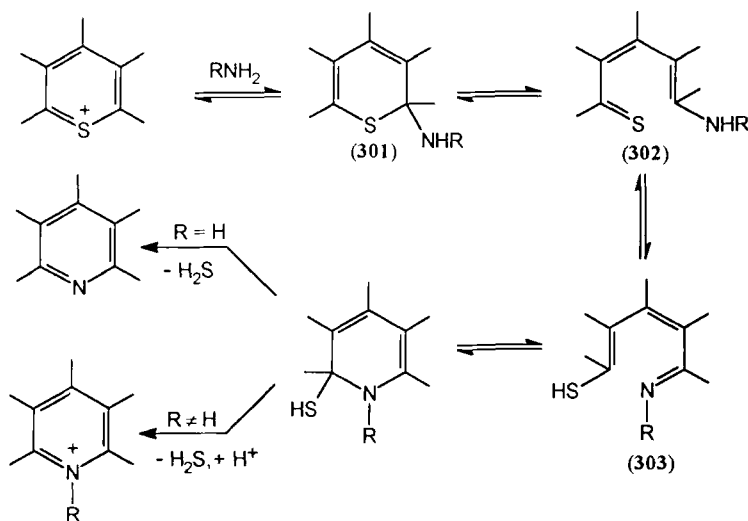
In some cases, despite the presence of a leaving group, other reactions take place. Thus 4-chlorothiopyrylium ion (**145**) reacts with dimethylamine to give the ring-opening product **300** ($R^1 = R^2 = \text{Me}$, $R^3 = \text{Cl}$). This is probably formed by initial nucleophilic attack at the α position followed by ring-opening, attack of a second molecule of dimethylamine, and elimination of hydrogen sulfide. Interestingly, **145** gives the normal substitution product with aniline or *N*-methylaniline (75T2669). A further example is offered by the reaction of 4-methoxythiopyrylium ion (**142**) with aqueous ammonia that gives 4-methoxypyridine instead of the substitution product (63ZOB1864).



The unsubstituted thiopyrylium ion (**2**) reacts with various primary and secondary amines under mild conditions to yield a symmetrical 5-amino-

2,4-pentadienyliminium cation **300** ($R^1 = H$, $R^2 = Ph$, substituted-Ph, Me; $R^1 = Me$, $R^2 = Ph$, Me; $R^1, R^2 = morpholino$; $R^3 = H$) in all trans configuration (73JOC3990). The proposed mechanism is the same as that for the formation of **300** ($R^1 = R^2 = Me$, $R^3 = Cl$).

Thiopyrylium ions, by reaction with ammonia or primary amines, can be converted into pyridine or pyridinium ions, respectively. The mechanism, which is believed to be analogous to that commonly accepted for the conversion of pyrylium salts into pyridines or pyridinium ions [82AHC(S)106-27], is shown in Scheme 22. The initially formed 2-amino-2*H*-thiopyran **301** would undergo a thermally allowed ring-opening to yield a divinyllogous thioamide **302**, which then isomerizes to an imino-thioenol **303**. Recyclization of the latter, followed by loss of hydrogen sulfide, would afford the final pyridine or pyridinium ion. Despite the similarities, the conversion of thiopyrylium ions into pyridine derivatives is not as broad in scope as that of pyrylium ions. This is well illustrated by the reaction of the monomethine cyanine dye **11** ($Z = O$, $Y = S$, $n = 0$) with ammonia in pyridine or with alcoholic methylamine; in both cases the oxygen atom is selectively replaced yielding the corresponding pyridine derivative **11** ($Z = N$, NMe, $Y = S$, $n = 0$) (76JHC577). Some examples of $S \rightarrow N$ exchange have been already cited. 2,4,6-Triarylthiopyrylium ions react with methylamine affording the corresponding *N*-methylpyridinium ions (56HCA207; 73JOC3990; 82JOC3496), but, in contrast with the corresponding oxygen analogs, do not react with aniline (56HCA207;

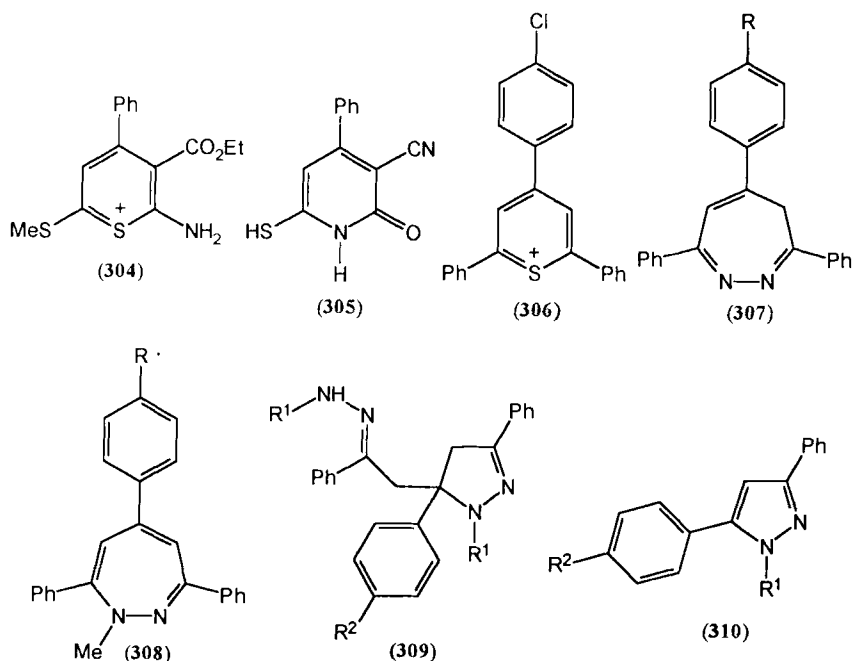


SCHEME 22

73JOC3990), unless 1 equiv. of a tertiary amine, such as triethylamine, is added (82JOC3496). The reaction of 2,4,6-triphenylthiopyrylium cation (**9**) with one equiv. of aniline and one of triethylamine in Me_2SO yields the corresponding 2-anilino-2*H*-thiopyran, which is slowly converted at room temperature into the 1,2,4,6-tetraphenylpyridinium ion (82JOC3496). Conversion of phenyl-substituted thiopyrylium salts into the corresponding pyridines has also been carried out by reaction with pyridinium-*N*-imide ($\text{C}_5\text{H}_5\text{N}^+ - \text{NH}^-$) (80NKK604). 2,4-Diphenylthiopyrylium ion (**154**) reacts with methylamine in ethanol or dimethylformamide to yield only 12–18% of the corresponding *N*-methylpyridinium ion, the principal product probably being 4,6-diphenyl-2*H*-thiopyran (Section IV,C,8) [80JCS(P1)1345]. Aromatic amines behave as C-nucleophiles toward 2,6-diphenyl- (**18**) and 2,4-diphenyl-thiopyrvlium (**154**) ions (Section IV,C,7).

A complex reaction involving a $\text{S} \rightarrow \text{N}$ exchange is that transforming the thiopyrylium cation **304** into the 2-pyridone **305** by treatment with ethanolic ammonia (73JPR679).

The reactions of the triarylthiopyrylium salts **9**, **66**, and **306** with hydrazine and hydrazine derivatives can lead to either ring-expansion or ring-contraction products (74CJC2798). Treatment of the above triarylthiopyrylium salts with an excess of hydrazine in ethanol solution gave the

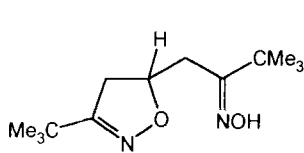


1,2(4*H*)-diazepine derivatives **307** ($R = H, NMe_2, Cl$) in good yield. Addition of the thiopyrylium salts to an excess of neat methylhydrazine at $-70^\circ C$ followed by further reaction at $0^\circ C$ gave the 1-methy-1,2(1*H*)-diazepines **308** ($R = H, NMe_2, Cl$). If great care is not taken to remove excess methylhydrazine immediately after the reaction, the observed products are pyrazoline derivatives rather than 1,2(1*H*)-diazepines. For example, pyrazolines **309** ($R^1 = Me, R^2 = H, NMe_2$) were obtained under these conditions. Under the conditions that afforded diazepines **308**, the reaction of **9** and **306** with phenylhydrazine gave only the pyrazolines **309** ($R^1 = Ph, R^2 = H, Cl$). Thermolysis of the pyrazolines **309** ($R^1 = Me, R^2 = H, NMe_2$; $R^1 = Ph, R^2 = H, Cl$) afforded the corresponding pyrazoles **310**. The pyrazoles **310** ($R^1 = Ph, R^2 = H, Cl$) could also be obtained directly by carrying out the reaction between **9**, or **306**, and phenylhydrazine in benzene suspension.

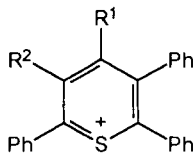
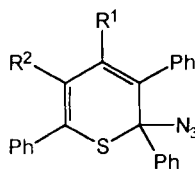
The formation of 1,2-diazepine by reaction of thiopyrylium salts with hydrazine hydrate in an organic solvent has also been patented (85EGP218360).

A ring-contraction also occurs in the reaction of 2,6-di-*tert*-butylthiopyrylium ion (**26**) with hydroxylamine to give the isoxazoline **311** in excellent yield [90ZN(B)701].

The reaction between thiopyrylium salts and sodium azide has been studied by Desbene and co-workers both experimentally and theoretically [75CR(C)(280)37; 84T3539, 84T3549]. Paradoxically, whereas cations **312–314** react with azide ion in acetonitrile to give the corresponding 2*H* adducts **315–317**, less crowded cations give only charge-transfer complexes (Section II,C,1,c). Various attempts to convert the charge-transfer complexes into azido-2*H*-thiopyrans were unsuccessful, thus suggesting that they are not along the reaction path leading to the adducts. The azido-2*H*-thiopyrans, on heating, form unstable thiazepins, which decompose competitively to yield pyridines after sulfur extrusion and thiophenes after elimination of benzonitrile. Photochemical attempts to obtain thiazepins from azidothiopyrans were unsuccessful [75CR(C)(280)37; 84T3559].



(311)

(312) $R^1 = H, R^2 = Ph$ (313) $R^1 = Ph, R^2 = H$ (314) $R^1 = R^2 = Ph$ (315) $R^1 = H, R^2 = Ph$ (316) $R^1 = Ph, R^2 = H$ (317) $R^1 = R^2 = Ph$

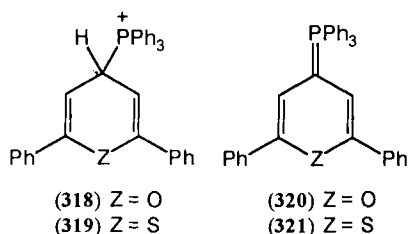
The reaction between phenyl-substituted thiopyrylium salts and sodium azide has been studied by other authors as well (80NKK604).

6. Reactions with Phosphorus Nucleophiles

Few studies have been reported about the reaction of chalcogenopyrylium salts with phosphorus nucleophiles.

2,6-Diphenyl-pyrylium (**17**) and -thiopyrylium (**18**) ions react with triphenylphosphine in either nitromethane or acetonitrile to yield exclusively the 4*H* adducts **318** and **319**, respectively (69KGS368; 80JOC2458). The reaction is reversible and the degree of dissociation of the adducts depends on the electron acceptor properties of the heteroaromatic cations; i.e., the more easily reducible thiopyrylium cation gives the more stable adduct (89ZOB1506). The structure of **318** has been confirmed by X-ray investigation, thus excluding the possibility that the phosphine adduct is a charge-transfer complex (89ZOB1506).

By treating the cation **17** or **18** with triphenylphosphine (also in a catalytic amount) in pyridine, the symmetrical bipyranilidenes **14** ($Z = O, S, R = Ph$) have been obtained in good yield (79JOC4456). The authors suggest that the reaction occurs through the formation of a Wittig intermediate (**320** or **321**), which on warming couples to give **14** ($Z = O, S, R = Ph$) and triphenylphosphine.



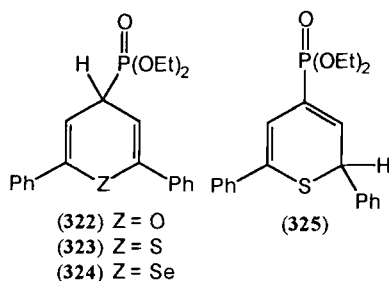
The reaction has been successfully carried out also with 2,6-di-*tert*-butylthiopyrylium (**26**) and selenopyrylium (**27**) (87JOC2123), but not with the corresponding pyrylium ion (**25**), which apparently does not form a phosphonium salt with triphenylphosphine (79JOC4456).

The symmetrical bipyranilidenes **14** ($Z = O, S, R = Ph$) can be also obtained by reacting the phosphonium salt **318** or **319** with butyllithium at -78°C in THF for 45 min. However, if the preparation of the Wittig reagent is limited to 5–10 min and is followed by the addition of a γ -unsubstituted pyrylium or thiopyrylium salt, different from that utilized in the preparation of the starting phosphonium salt, unsymmetrical bipyranilidenes can be obtained (80JOC2458).

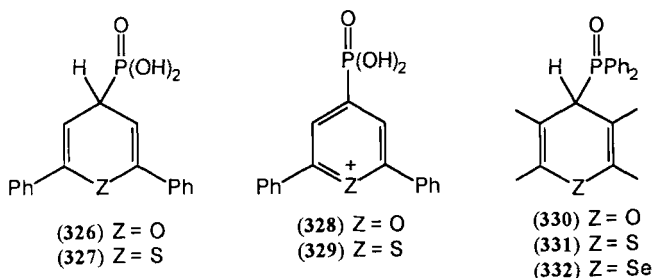
2,6-Disubstituted telluropyrilium cations **20** and **28** with triphenylphosphine in pyridine under aerobic conditions, or with triphenylphosphine oxide with exclusion of air, gave an oxidative dimerization to produce 1,1-dioxo(telluropyranylidene)telluopyrans **272** and **273**, respectively (Section IV,C,2).

2,6-Diphenyl-substituted chalcogenopyrylium ions **17–19** react with sodium diethyl phosphonate $[(\text{EtO})_2\text{P}(=\text{O})\text{Na}]$ in dry ether to yield the pyranylphosphonates **322–324**, respectively. These can be deprotonated by potassium *tert*-butoxide in THF to give the corresponding Horner–Emmons reagent, which with carbonyl compounds readily undergoes the olefination reaction. By protonation of the formed anhydrobases, γ -alkyl chalcogenopyrylium cations can be obtained (73ZOB359).

The thiopyranyl phosphonate **323** has been isolated by other authors as a colorless solid, which in a few weeks turns to a brown viscous oil (80JOC2453). This behavior is due to the partial isomerization of **323** to the *2H* isomer **325**. Compound **323** has been lithiated by butyllithium in THF at -78°C . The *4H*-lithiated species is a kinetically controlled product that equilibrates to the more stable *2H*-lithiated species even at -78°C . The *4H* anion, as previously shown by Krivun and co-workers (73ZOB359), can react with carbonylic compounds, providing a convenient synthetic route to 4-alkylidene-2,6-diphenylthiopyrans (80JOC2453; 81JHC627).



The reaction of trimethyl phosphite with sodium iodide in acetonitrile, when tried on 2,6-diphenylthiopyrylium cation (**18**), failed to give the desired phosphonate **323** (80JOC2453). It has been reported, however, that 2,6-diphenyl-pyrylium (**17**) and -thiopyrylium (**18**) bromides react with triethyl phosphite to give the diethyl phosphonates **322** and **323**, respectively (71DOK600). These can be hydrolyzed with HCl to give the pyranyl- and thiopyranyl-phosphonic acids **326** and **327**, which treated with triphenylmethyl perchlorate give the pyrylium- and thiopyrylium-4-ylphosphonic acids **328** and **329**.

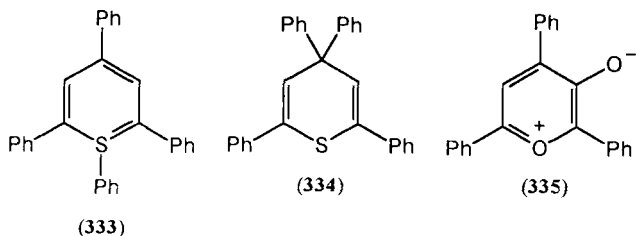


A number of variously substituted chalcogenopyranyldiphenylphosphine oxides, **330–332**, have been prepared by reaction of the corresponding γ -unsubstituted heteroaromatic cations with methyl diphenylphosphinite (Ph_2POMe) in acetonitrile in the presence of sodium iodide (90ZOB1012).

7. Reactions with Carbon Nucleophiles

The reactions of chalcogenopyrylium salts with carbon nucleophiles can be divided in two main groups, i.e., the reactions involving ring-opening and those not involving ring-opening. In turn the latter reactions can be subdivided into reactions leading to charge-transfer complexes, additions, substitutions, and oxidative substitutions. Apart from the reactions leading to the formation of charge-transfer complexes, reported in Section II,C,1,c, the most simple reactions are those leading to stable addition products, and these will be treated first.

Organometallic reagents normally give addition reactions. The most peculiar reaction of thiopyrylium salts is that leading to the formation of thiabenzene derivatives via nucleophilic addition to the sulfur atom. The first thiabenzene, **333**, was prepared by reaction of 2,4,6-triphenylthiopyrylium ion (**9**) with phenyllithium in ether under an atmosphere of nitrogen. It was an amorphous purple compound, which rearranged to its 4*H*-thiopyran isomer **334** on standing at room temperature under nitrogen and reacted readily with oxygen to yield, after treatment with hydrogen

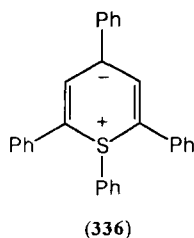


chloride, the mesoionic pyrylium derivative **335** and thiophenol (61JA1770; 62JA2094).

Attempts to isolate 1-cyclopentadienyl-, 1-phenylethynyl-, and 1-alkyl-2,4,6-triphenyl-thiabenzene by reaction of **9** with alkyllithiums or Grignard reagents have been unsuccessful and only 2*H*- and/or 4*H*-thiopyrans have been obtained. However, a transient intense coloration of the reaction solutions has been taken as evidence that the primary nucleophilic attack is at the sulfur atom (62JA2090; 71JOC791). Contrarily to aryllithiums, arylmagnesium halides do not allow the isolation of thiabenzene but only of 2*H*- and 4*H*-thiopyran adducts (72JOC1718).

The claimed preparation of the simple 1-phenylthiabenzene (69JA1206) and of some benzofused thiabenzene has been disproved by Mislow and co-workers (75JA2718). The reason for such failure seems to be mainly ascribable to proton abstraction from the α position of the thiopyrylium ring by phenyllithium, to generate a thiopyrylium ylide that may be the source of unidentified reaction products.

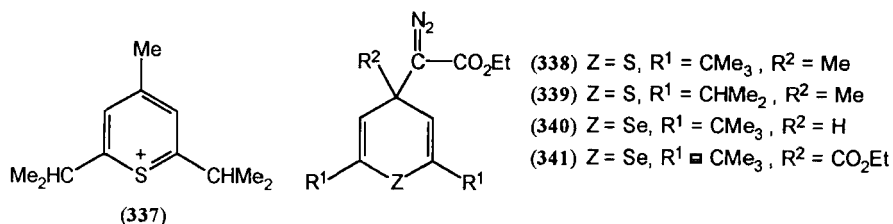
NMR measurements suggest that the structure of thiabenzene is best described as a sulfonium ylide, e.g., **336**, with a barrier to pyramidal inversion of sulfur of at least 23 kcal mol⁻¹ (70JA1803; 74JA6119; 75JA2718). The ylide structure is consistent with the fact that electron-donating groups on the phenyl ring attached to sulfur, contrarily to those on phenyl rings attached to the α and γ carbons, increase the stability of 1,2,4,6-tetraarylthiabenzene (71JOC791; 72JOC1718; 76JHC237). As expected, electron-withdrawing groups exert the opposite effect (77JHC199). In addition to the electronic effects, replacement of the 3- and 5-hydrogen atoms of the sulfur ring in **333** with a bulky group such as methyl decreases the stability of the thiabenzene (75JA2718). The results of a mechanistic investigation of the rearrangement of *S*-aryl thiabenzene to their isomeric thiopyrans indicate an intramolecular rearrangement that involves a 1,2- or 1,4-migration of *S*-aryl groups (79JHC917).



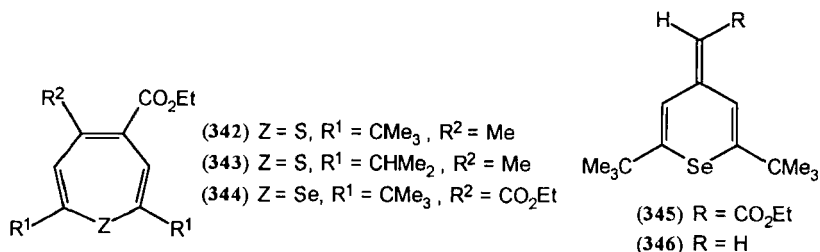
The addition of Grignard reagents or alkyllithium to thiopyrylium salts yields 2*H*- and/or 4*H*-thiopyran adducts with an apparently unpredictable

regioselectivity, unless one of the α or γ positions is unsubstituted [62JA2090, 62LA189; 64LA183; 71JOC791, 71KGS(S)85; 83JOC2757]. In that case the addition usually takes place exclusively at these less hindered positions (68KGS762; 70KGS338, 70ZOR1513; 71ZOR613; 74KGS489; 79JA5059; 80MI5). Selenopyrylium ions behave analogously (82MI6). Even the nature of the thiopyrylium counter-ion may play a role on the regioselectivity of Grignard addition. For example, the reaction of 2,4,6-triphenylthiopyrylium perchlorate with benzylmagnesium chloride affords a mixture of the corresponding *2H*- and *4H*-thiopyrans, whereas under the same conditions 2,4,6-triphenylthiopyrylium iodide gives exclusively the *4H*-thiopyran (72JOC150). The addition of methylmagnesium iodide to the unsubstituted thiopyrylium cation (2) affords a complex mixture composed of 2-methyl-*2H*-thiopyran, 4-methyl-*4H*-thiopyran, 4-methyl-*2H*-thiopyran, *2H*-thiopyran, *4H*-thiopyran, and another unidentified product (67G397).

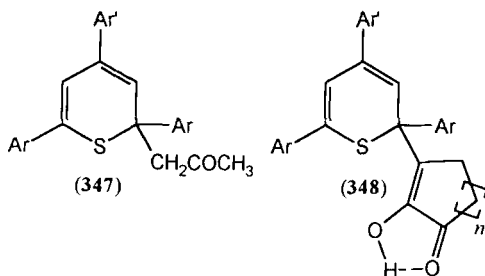
Ethyl lithiodiazoacetate generated in THF–ether at -120°C reacts with the thiopyrylium cations **62** and **337**, and with the selenopyrylium cations **27** and **129**, to yield the corresponding *4H*-chalcogenopyranyl diazoesters **338–341** [78CL723; 79JA5059; 80MI5; 90AG(E)424]. By treatment with



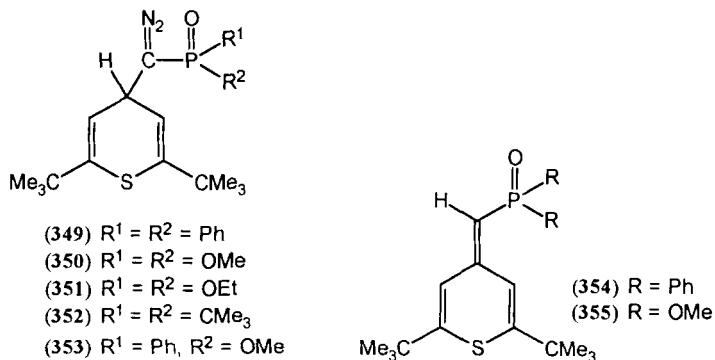
di- μ -chlorobis-(π -allyl)palladium(II), compounds **338** and **339** yield the corresponding thiepins **342** and **343** and compound **341** yields the selenepine **344**, whereas compound **340** yields the anhydrobase **345**. The reaction between ethyl lithiodiazoacetate and the selenopyrylium cation **63**, instead of the expected *4H* adduct, yields the anhydrobase **346**.



Besides organometallic reagents, compounds possessing active methyl (ene) groups can give addition products. Thus 2,4,6-triarylthiopyrylium salts react with acetone in the presence of amine salts of weak acids (e.g., piperidinium acetate) to give 2-acetonyl-2*H*-thiopyrans **347** (Ar, Ar' = Ph or substituted Ph) (86EGP235455, 86JPR573). 2*H*-Thiopyrans **348** (Ar, Ar' = Ph or substituted Ph, $n = 1, 2$) are similarly obtained by reaction of 2,4,6-triarylthiopyrylium salts with 1,2-cyclopentanedione or 1,2-cyclohexanedione (89JPR853; 90EGP280324).



Phosphoryl diazomethanes react with 2,6-di-*tert*-butylthiopyrylium ion (**26**) in the presence of triethylamine to give the corresponding 4-(diazomethyl)-4*H*-thiopyrans **349–353**. Reaction of compound **349** or **350** with di- μ -chlorobis-(π -allyl)palladium(II), instead of the expected thiopine derivative, afforded the anhydrobase **354** or **355**, respectively (85T811).



In some cases, 2*H* or 4*H* adducts are isolable intermediates of substitution or oxidative substitution reactions (see below).

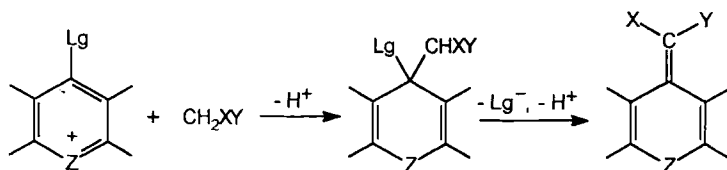
Substitution reactions require the presence of a good leaving group in the α or γ position of a chalcogenopyrylium salt. Usually the leaving group is a halogen, an alkoxy, or an alkylthio group, and the nucleophiles are

compounds possessing active methyl or methylene groups. In these cases the reaction proceeds according to Scheme 23. Thus 4-chlorochalcogenopyrylium salts react with 1,3-cycloalkanediones (75CB2397; 76CB1549), 3-oxo-1-thiacycloalkane 1,1-dioxides (75CB2397), 1,2,3,4-tetraphenylcyclopentadiene (75CB2397), ethyl malonate (75CB2397), nitromethane (75CB2397), lithium phenalenide (71TL4799), 2-phenyl-2-oxazolin-5-one (74URP410016; 76KGS764), and 4-azolidones (80MI7) to yield the corresponding anhydrobases. Analogous substitutions are given by 4-methoxythiopyrylium ion (**142**) reacting with malononitrile, ethyl cyanoacetate, and cyanoacetamide in the presence of potassium *tert*-butoxide (74MI1), and by 4-ethoxy-2,6-diphenyltelluropirylium reacting with Meldrum's acid in pyridine (82JOC5235). Analogously 2-methylthiothiopyrylium salts react with 2,4-pentanedione, 1,3-indanedione, benzoylacetonitrile, (m)ethyl cyanoacetate, malononitrile, cyanoacetamide, ethyl acetylacetate, ethyl benzoylacetate, ethyl malonate, 5-phenyl-2,3-dihydrothiophen-3-one, and 3-methyl-1,2-dithiolylium cations to yield the corresponding anhydrobases [74BSF1196, 74BSF1356; 75JPR561; 80BSF(2)423, 80BSF(2)577]. In the reaction with the latter reagent the intermediate 2*H*-thiopyrans can be isolated if AcOH, instead of butanol, is used as reaction solvent [80BSF(2)577].

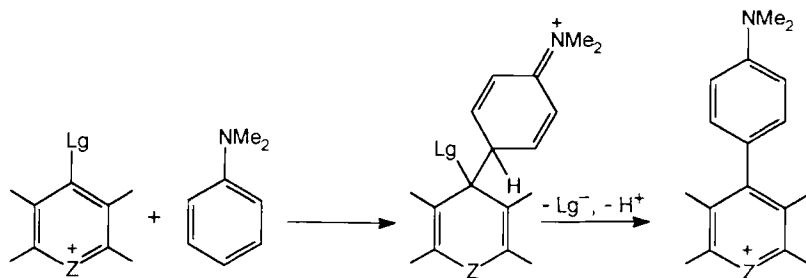
2-Morpholino-thiopyrylium salts **94** ($R^1 = \text{Ph}$, $p\text{-MeC}_6\text{H}_4$, $p\text{-MeOC}_6\text{H}_4$, $R^2 = \text{H}$) undergo the substitution of the morpholino group with methyl cyanoacetate and malononitrile (71JPR1113).

The reaction of 2-methylthio-4,6-diphenylthiopyrylium (**159**) with benzoylacetic acid involves, after the condensation step, a decarboxylation step yielding an anhydrobase of the type **261** ($R = \text{Ph}$). The same reaction is also given by 4-methylthio-2,6-diphenylthiopyrylium (**162**) [70JCS(C)1202]. Analogously, the reaction of 2-methylthiothiopyrylium salts with malonic acid proceeds through two sequential condensation and decarboxylation steps, yielding thiopyrylomonomethine dyes (e.g., **18a**) [80BSF(2)434].

In some substitutions the nucleophile is an activated aromatic compound; in these cases a good leaving group, such as a halogen, is required. These reactions proceed as exemplified in Scheme 24 for the case of



SCHEME 23



SCHEME 24

dimethylaniline. Thus 4-chlorothiopyrylium salts undergo substitution by dimethylaniline, 1-alkylindoles (attack occurs at position 3 of the indole ring), anthrone, and 2,6-di-*tert*-butylphenol (68CB3990; 71KGS1320; 73MI1). 2-Chloro-4,6-diphenylthiopyrylium ion (**146**) undergoes an analogous substitution by dimethylaniline (69JPR61).

Chlorothiopyrylium ions can also be formed *in situ*. Thus the thiopyrylium ion **267** has been prepared by reaction of 2,6-diphenyl-4*H*-thiopyran-4-one [**140** ($Z = S$, $R = Ph$)], $POCl_3$ and the appropriate anilino derivative (83HCA2165). An analogous reaction occurs between the thiopyran-2-thione **164**, $POCl_3 + PCl_5$, and 2,4-diphenylthiophene as an activated aromatic compound [77JCS(P1)1511].

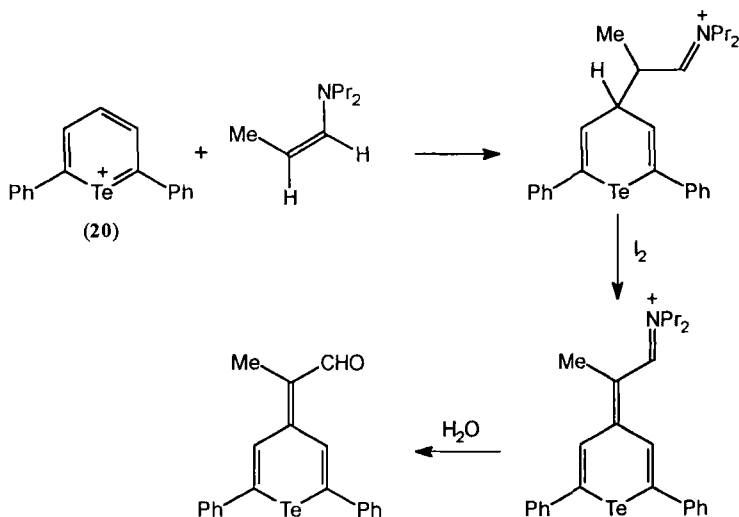
Certain substitution reactions have been described in previous sections: those in which the active methyl(ene) compound is an alkylchalcogenopyrylium salt have been described in Section IV,B,1; thermal decomposition of 2-acylmethylthiopyrylium salts, which can be viewed as an intramolecular substitution, has been described in Section IV,B,2.

Oxidative substitutions differ from the normal substitutions reported in Schemes 23 and 24 in two ways: (a) a hydrogen atom that takes the place of the leaving group and (b) the presence of an oxidant that formally abstracts hydride from the chalcogenopyran intermediate. Often the chalcogenopyrylium ion functions as both substrate and hydride acceptor (autooxidative substitutions). Thus 2,6-diphenylthiopyrylium ion (**18**) undergoes the autooxidative substitution with 1,3-indanedione, 3-methyl-1-phenyl-2-pyrazolin-5-one, barbituric acid, rhodanine, aniline and aniline derivatives, antipyrine, 2,3-dimethylbenzoxazolium, 2,3-dimethylbenzothiazolium, 2,3-dimethylbenzoselenazolium, 1,2,3,3-tetramethylindolium, 2,5-dimethyl-1,3-benzodithiolium, and 4-methyl-2,6-diphenylthiopyrylium (66HCA2046). Cation **18** gives the products of autooxidative substitution with 6-membered cyclic β -diketones, whereas with the 7- to 12-membered 1,3-cycloalkanediones the corresponding products of simple γ addition can be isolated. The latter products can be dehydrogenated

by 2,4,6-triphenylphenoxy-catalyzed oxidation with cyanoferrate(III) to yield the corresponding anhydrobases (76CB1549). Other autoxidative substitutions include the reaction of 2,6-diphenylthiopyrylium (**18**) or selenopyrylium (**19**) cations with 2-phenyl-2-oxazolin-5-one formed *in situ* by heating hippuric acid in Ac_2O containing AcONa (74MI2; 75URP465402); the reaction of cation **19** with *N,N*-dimethylaniline and 1-methylindole (74KGS1174); the reaction of 2,6-di-*tert*-butylthiopyrylium cation (**26**) with *N,N*-dimethylaniline (86JA3409); the reaction of 2,4-diphenylthiopyrylium cation (**154**) with 2-aminopyridines, aniline, and aniline derivatives [80JCS(P1)1345; 81BRP2070605; 83USP4368329]. 2,6-Diphenylthiopyrylium cation (**18**) reacts with malonic acid, glutamic acid, and 2,4-eptadienedioic acid to yield the products of autoxidative substitution and decarboxylation, namely the cyanine dyes **11** ($Z = Y = \text{S}$) with $n = 0, 1, 2$, respectively (66HCA2046). The reaction with malonic acid has been extended to 2,6-diphenylselenopyrylium ion (**19**) (75URP484215).

Other autoxidative substitutions in which the nucleophile is a derivative of a chalcogenopyrylium ion have been described in Section IV,B,1.

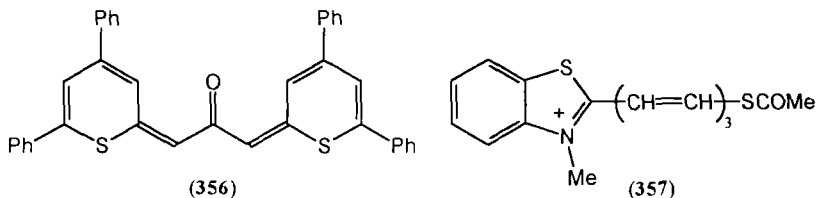
Enamines, generated *in situ* by iodine oxidation of tertiary amines, can react with α - or γ -unsubstituted chalcogenopyrylium ions yielding the corresponding chalcogenopyranylidene iminium salts, which are easily hydrolyzed to chalcogenopyranylidene aldehydes or ketones (84JOC2676). The reaction proceeds as exemplified in Scheme 25 for 2,6-



SCHEME 25

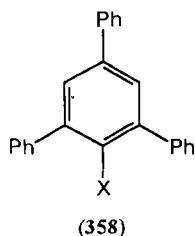
diphenyltelluropyrilium ion (**20**) and the enamine derived from tripropylamine. In the reaction of 2,6-di-*tert*-butylselenopyrylium ion (**27**) with the same enamine, the intermediate 4*H*-selenopyran was oxidized by iodine only in part, the final product consisting in a mixture of 4*H*-selenopyranyl and 4*H*-selenopyranylidene aldehydes. 2,4-Diphenylthiopyrylium ion (**154**) reacts with triethylamine and iodine to yield the expected aldehyde, but reacts with *N,N*-diisopropylmethylamine to yield the ketone **356** resulting from a double substitution. Electron-withdrawing substituents attached to the trialkylamine greatly reduced the efficiency of the reaction. In fact, the only substrate that gave isolable amounts of aldehyde in the reaction with 2-cyanoethyl-*N,N*-dimethylamine was 2,6-di-*tert*-butyltelluropyrilium ion (**28**).

A certain number of reactions of thiopyrylium salts with active methyl(ene) compounds involve ring-opening. Thus, treatment of unsubstituted thiopyrylium (**2**) with 2,3-dimethylbenzothiazolium ion in Ac_2O in the presence of pyridine yields compound **357**. It is apparent that the thioenol initially formed on ring fission is acetylated in the reaction medium (65ZOB316). Analogous products are obtained in the reaction of 2-methyl-3-ethylbenzothiazolium, 2-methyl-3-ethyl-6,7-benzobenzothiazolium, *N*-phenylrhodanine, and 3-methyl-1-phenyl-2-pyrazolin-5-one with 4-methoxythiopyrylium ion (**142**), despite the presence of a potential leaving group in the γ position (63ZOB1864).



2,4,6-Triarylthiopyrylium ions can react with active methyl(ene) compounds to yield substituted benzenes according to the addition of nucleophile–ring opening–ring closure (ANRORC) mechanism. Thus 2,4,6-triphenylthiopyrylium ion (**9**) reacts with the CH acids CH_2XY ($\text{X} = \text{CN}$, $\text{Y} = \text{CN}$, CONH_2 , CO_2Et ; $\text{X} = \text{Y} = \text{COMe}$; $\text{X} = \text{CO}_2\text{Et}$, $\text{Y} = \text{COMe}$) in $\text{Bu}'\text{OH}$ in the presence of $\text{Bu}'\text{OK}$ to yield 2,4,6-triphenylbenzene derivatives **358** (71T6083). Interestingly, in the reaction of **9** with nitromethane, a final alkali treatment gave compound **358** with $\text{X} = \text{NO}_2$, whereas a final acid treatment afforded compound **358** with $\text{X} = \text{H}$. Plausible mechanisms for these different behaviors have been proposed (71T6083).

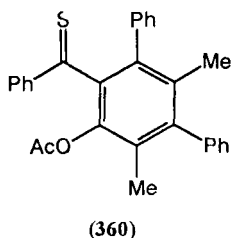
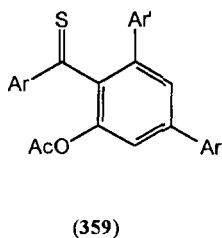
The reaction of **9** with malononitrile in ethanol in the presence of diisopropylethylamine afforded compound **358** with $\text{X} = \text{CN}$. The reaction



was extended to other 2,4,6-triarylthiopyrylium ions. A mechanism in which the sulfur atom is eliminated as thiocyanate has been proposed (71JHC301).

Reaction of **9** with nitromethane or ethyl cyanoacetate in the presence of triethylamine affords **358** with $X = H$ or CN , respectively (83ZC333; 86JPR373). The reaction with $MeNO_2$ and Et_3N has been also successfully carried out with cations **21** and **313** (87JPR975). By treating 2-acetyl-2*H*-thiopyran **347** ($Ar = Ar' = Ph$) with alcoholic alkali, a mixture of **358** with $X = H$ and $COMe$ is obtained (86JPR573).

The reaction of 2,4,6-triarylthiopyrylium salts ($2,6-Ar$, $4-Ar' = Ph$ or substituted Ph) with acetic anhydride in the presence of an appropriate condensing agent yields a mixture of the corresponding 1,3,5-triarylbenzenes and thiobenzophenones **359** (88EGP259398, 88JPR35). The recyclization mode for the formation of the first compound is 2,6- $[C_5 + C]$, whereas that for the formation of the second compound is 2,5- $[C_4 + C_2]$ [for classification of the various recyclization modes, see Balaban *et al.* (82AHC(S)87-89)]. Under the same conditions 3,5-dimethyl-2,4,6-triphenylthiopyrylium ion forms, via [1,5] sigmatropic rearrangement, the thiobenzophenone **360**.

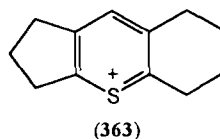
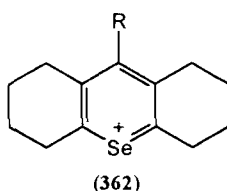
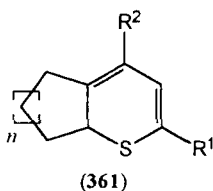


The reactions of thiopyrylium ions with sulfur ylides have been also investigated. Thus 2,4,6-triphenylthiopyrylium cation (**9**) reacts with $Me_2S^+(O)CH_2^-$ or with $MeS^+(R)CH^-COPh$ ($R = Me, Ph$) to yield compound **358** with $X = H$ or $COPh$, respectively [72Cl(L)498; 80NKK604]. The reaction with the latter reagents also occurs with 2,3,4,6-tetraphenylthiopyrylium cation (**313**) (80NKK604).

8. Reactions with Hydride Donors

The reduction of chalcogenopyrylium salts to chalcogenopyrans can be easily accomplished with complex hydrides. Reductions carried out with LiAlH_4 will be examined first. The reduction of unsubstituted thiopyrylium ion (**2**) with LiAlH_4 leads to a mixture of *2H*-thiopyran and *4H*-thiopyran in a 1:9 ratio (65MI3; 67G397). In contrast, 3,5-diphenylthiopyrylium ion gives an equimolar ratio of both *2H* and *4H* isomers (74JA6119). Thiopyrylium cations **77** ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Ph}, \text{PhCH}_2$, $n = 1$; $\text{R}^2 = \text{Ph}, p\text{-MeOC}_6\text{H}_5$, 3,4-(MeO) $_2\text{C}_6\text{H}_3$, $n = 2$) give the corresponding *6H*-thiopyrans **361** in yields of 25 to 73% accompanied, in some of the cases, by the corresponding *2H* and/or *4H* isomers (75ZOR2173). From the reduction of 2,4,6-triphenylthiopyrylium ion (**9**), the corresponding *4H*-thiopyran has been obtained in 54% yield (62JA2090). Thiopyrylium salts having substituents in positions 2 and 6, but not in 4, react with LiAlH_4 to yield exclusively *4H*-thiopyrans. This behavior is shown by 2,3,5,6-tetraphenylthiopyrylium ion (**312**) (71ZOR613; 84T3539), the bicyclic cations **77** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $n = 1, 2$) (74KGS489), and the tricyclic cation **79** ($\text{R} = \text{H}$, $n = 2$) (70ZOR1513). 2,6-Di-*tert*-butylselenopyrylium ion (**27**) [90AG(E)424] and octahydroselenoxanthylum ions **362** ($\text{R} = \text{H}, \text{Me}, \text{Et}, \text{Pr}, \text{Ph}, \text{PhCH}_2, p\text{-BrC}_6\text{H}_4$) react with LiAlH_4 to give the corresponding *4H*-selenopyrans (82MI6).

A number of reductions have been carried out with NaBH_4 . Reduction of 2,4,6-triphenylthiopyrylium ion (**9**) with NaBH_4 affords a 3:7 mixture of *2H* and *4H* isomers in methanol (91JOC1674) and a 1:1 mixture in acetonitrile [77ACS(B)496]. Other thiopyrylium cations that have been reduced with NaBH_4 in methanol are (*2H*:*4H* ratios given in parentheses) **18** (0:100), **111** (4:96), **26** (9:91), **46** (91:9), and **84** (31:69) (91JOC1674). The tricyclic cations **79** ($\text{R} = \text{H}$, $n = 1$) and **363** are reduced by NaBH_4 to the corresponding *4H*-thiopyrans (76ZOR1802). Pentaphenylthiopyrylium ion (**314**) undergoes reduction with LiBH_4 in THF to yield the corresponding *4H*-thiopyran in 30% yield (84T3539). The octahydroselenoxanthylum ions **362** ($\text{R} = \text{H}, \text{Me}, \text{Et}, \text{Pr}, \text{Ph}, \text{PhCH}_2, p\text{-BrC}_6\text{H}_4$) react with NaBH_4 to give the corresponding *4H*-selenopyrans (82MI6).

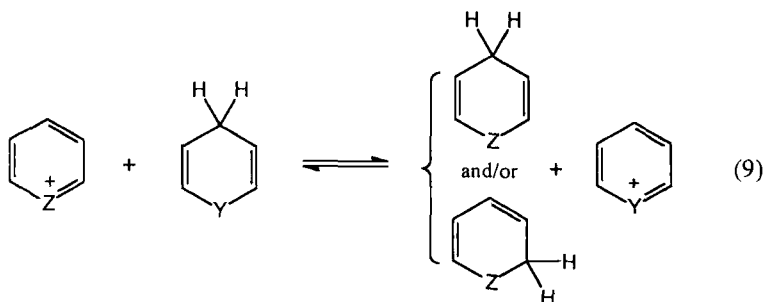


2,6-Di-*tert*-butyltelluropyrilium ion (**28**) is reduced by diisobutylaluminum hydride (DIBAL-H) to give the corresponding 2*H*- and 4*H*-telluropyrans in a 7:93 ratio and 90% overall yield, and less than 1% of dimer **13** ($Z = \text{Te}$, $R = \text{Bu}^t$). The addition of 0.5 equiv. of water to 1 equiv. of DIBAL-H followed by the addition of 1 equiv. of **28** and a second equiv. of DIBAL-H gives an 80:20 mixture of (2*H* + 4*H* isomers) to **13** (88MI4).

Hydride ion may be provided not only by complex hydrides as described above, but also by organic molecules through hydride transfer reactions. Thus, treatment of the tricyclic cation **79** ($R = \text{H}$, $n = 2$) with 1,3-dimethylbenzimidazoline for 48 hr in diethyl ether gives 70% of **123** and 79% of the 1,3-dimethylbenzimidazolium cation (74IZV1831).

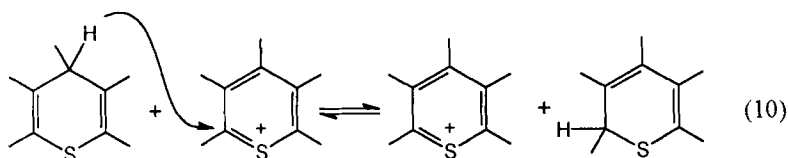
2,4-Diphenylthiopyrylium cation (**154**) is reduced by methylamine, ethylamine, benzylamine, or triethylamine in ethanol to give 12–72% of a highly insoluble and nonvolatile compound, the elemental analysis for which was consistent with its formulation as 4,6-diphenyl-2*H*-thiopyran, but which may be an oligomer of this structure [80JCS(P1)1345].

Hydride transfer equilibria between unsubstituted chalcogenopyrylium ions and unsubstituted 4*H*-chalcogenopyrans have been studied in nitromethane solution. For the cases $Z = \text{O}$, $Y = \text{S}$, and $Z = \text{Se}$, $Y = \text{S}$, the equilibrium shown by Eq. (9) is completely shifted to the right, whereas for the cases $Z = \text{O}$, $Y = \text{Se}$, and $Z = \text{Se}$, $Y = \text{O}$, the equilibrium constant is practically 1 (65MI1). Analogously, the octahydrothioxanthylum ion [**79** ($R = \text{H}$, $n = 2$)] is obtained when thioxanthene **123** is treated with the octahydroxanthylum ion (76IZV612). Assuming that such equilibria are essentially driven by the relative stability of the heterocyclic cations, the following order of stability results: thiopyrylium > pyrylium \approx selenopyrylium. The greater stability of thiopyrylium ion is probably due to the best compromise between electronegativity and effectiveness of π -overlap between the heteroatom and the carbon π -framework. Analogous equilibria in acetonitrile between chalcogenochromenylium ions and the corresponding unsubstituted 4*H*-chalcogenopyrans



are completely shifted to the right, indicating that chalcogenopyrylium ions are more stable than the corresponding benzo-analogs (65MI1).

Thiopyrylium ions can function as catalyst in the equilibrium isomerization between the corresponding 2*H*- and 4*H*-thiopyrans, by abstracting a hydride ion as shown in Eq. (10) [77ACS(B)496; 91JOC1674]. Such isomerization equilibria have also been studied theoretically by MNDO and AM1 methods (91JOC4431). The kinetics of isomerization of 2,4,6-triphenyl-4*H*-thiopyran in the presence of 2,4,6-triphenylthiopyrylium ion has been investigated in DMF at various temperatures (81JHC1517).



Hydride abstraction of chalcogenopyrylium ions also occurs in the processes of autoxidative substitution. These are described in Sections IV, B, 1 and IV, C, 7.

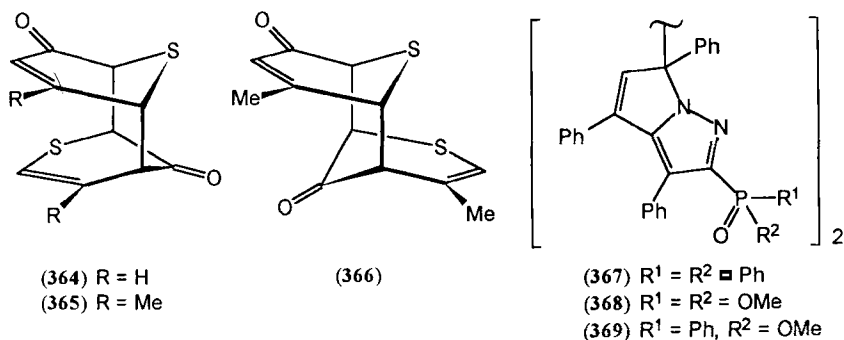
D. OTHER REACTIONS

3-Hydroxythiopyrylium ion (**194**) treated with triethylamine in THF undergoes proton abstraction and dimerization to yield *syn*-3,11-dithiatricyclo[5.3.1.1^{2,6}]dodecane (**364**). The 5-methyl analog **107** under the same conditions gives a mixture of the corresponding *syn* (**365**) and *anti* (**366**) dimers in the ratio 12 : 1. The dimers have a 1-thiacyclohexan-4-one ring that in the *syn*-isomer is locked in the boat conformation, and in the *anti*-isomer in the chair conformation. The preferential formation of the *syn*-isomer may be associated with secondary orbital overlap from the olefinic π -orbitals in the transition state [75ACS(A)453, 75JCS(P1)2099].

A complex ring transformation, probably involving radical intermediates, occurs in the reaction of 2,4,6-triphenylthiopyrylium ion (**9**) with the 4-(diazomethyl)-4*H*-thiopyrans **349**, **350**, and **353**, the reaction products being the bis(6*H*-pyrrolino[1,2-*b*]pyrazoles) **367**–**369**, respectively (85T811).

The unsubstituted thiopyrylium ion (**2**) undergoes the Diels–Alder reaction with cyclopentadiene as shown in Scheme 26 (74MI1).

2,4,6-Triphenylthiopyrylium ion (**9**) has been found to sensitize the *cis*-*trans*-photoisomerization of stilbene yielding 98% of *trans*-stilbene at photostationary state (67CC1165). The ability of thiopyrylium ions to function



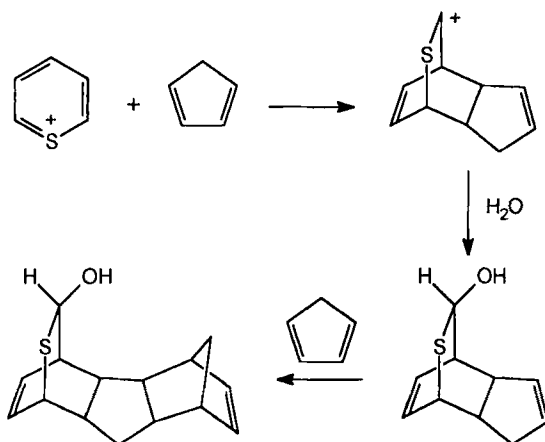
as effective photosensitizers has been exploited in numerous applications (Section V).

Charge-transfer complexes involving chalcogenopyrylium ions have been described in Section II,C,1,c.

V. Practical Applications

The number of patents and applicative studies making use of a chalcogenopyrylium salt is so vast that it will not permit a detailed coverage of them in this review. However, we have attempted to spotlight some of these studies to give a feeling of the many fields in which chalcogenopyrylium salts find application.

Most applications of chalcogenopyrylium salts exploit their photophysical and photochemical properties, and principally regard photographic and



SCHEME 26

reprographic technologies. In particular a large number of technological studies and patents involving chalcogenopyrylium salts deal with their application in the preparation of photosensitive compositions for electrophotographic photoconductors (thiopyrylium salts: 63BEP623972; 69BRP1153506, 69SAP69-949; 71USP889022; 72USP904032; 75FRP226-9742; 76USP3958991; 77JAP77-52637, 77JCP5628, 77USP4002475; 78-GEP2733911, 78MI3; 79MI3; 80MI8; 81BRP2070605, 81GEP3031595, 81JAP81-35141, 81JAP81-121042, 81JAP143436; 82GEP3133006, 82USP-4327169; 83JAP58-181051, 83JAP58-220143, 83USP4368329, 82USP438-4034; 84JAP59-146061; 87GEP3630389; 88JAP63-303362; 89GEP3832903, 89GEP3832940, 89JAP01-126655; selenopyrylium salts: 69BRP1153506; 82USP4327169; 83JAP58-181051, 83JAP58-220143; 84JAP59-146061; 89GEP3832903; telluropyrylium salts: 82USP4365017) and optical recording media (thiopyrylium salts: 83JAP58-181688, 83JAP58-181689, 83JAP58-220143; 84NEP83-155; 85JAP60-73892; 86JAP61-143191; 87-JAP62-159358; 88EGP258009, 88JAP63-13792; 89JAP01-126655; selenopyrylium salts: 83JAP58-181688, 83JAP58-181689; 85JAP60-73892; 86JAP61-143191; 87JAP62-159358; 88JAP63-13792; telluropyrylium salts: 85JAP60-73892; 86USP4584258). Also important is the application of chalcogenopyrylium salts as polymerization and crosslinking photoinitiators, especially in the preparation of photoresists, printing plates, and photosensitive compositions for laser imaging (thiopyrylium salts: 68-FRP1551034; 72CCC1520; 77MI6; 79USP4139655; 81JAP81-48626, 81MI2; 82JAP8224935, 82JAP82-26678; 83JAP58-40302, 83MI2, 83NKK798, 83NKK1703; 84BEP897694, 84JAP5942205; 85JAP60-76503, 85MI5, 85NKK119; 86MI4; 87NKK1027; 88JAP63-278903, 88MI6; 89EUP319296, 89GEP3834960; selenopyrylium salts: 68FRP1551034; 84BEP897694, 84JAP59-142205; 85JAP60-76503). Other applications related to the photographic industry include the preparation of photographic films, sheets, emulsions, and gelatines (thiopyrylium salts: 65BEP649986, 65FRP1387433; 68FRP1522354; 70USP876007; 71GEP2035392, 71USP889014; 72USP-3671251, 72USP3679415; 78USP4089684; 85MI6; 91USP5019549; selenopyrylium salts: 65BEP649986, 65FRP1387433; 68FRP1522354; 72USP-3671251).

Chalcogenopyrylium salts can find application also as laser dyes (thiopyrylium salts: 80MI1; 82MI1; 83MI3, 83MI4; 84MI3; 87MI4; 91MI4), liquid crystals (thiopyrylium salts: 83MI5, 83MI6; 84SC775; 85JAP60-118788, 85JAP60-118789, 85JAP60-118790, 85JAP60-118791; 86MI5; 88EGP258009; selenopyrylium salts: 85JAP60-118788, 85JAP60-118789, 85JAP60-118791), organic conductors (Section II,D), and photovoltaic elements for solar cells (thiopyrylium salts: 77MI5; 78MI2, 78USP4125414; 82MI5). Telluropyrylium dyes hold promise in the conversion of solar

energy to chemical energy by allowing the photoproduction of hydrogen peroxide (90JA4086; 92MI1).

Chalcogenopyrylium salts also show biological activity and can find application in medicine. In particular they can behave as bactericides (thiopyrylium salts: 76KFZ73, 76KFZ80; 81KFZ38; 82URP666803), fungicides (thiopyrylium salts: 77KFZ72; 87KFZ824), reversible inhibitors of cholinesterases (thiopyrylium and selenopyrylium salts: 87DOK1499; 88MI7), chemotherapeutics for differentiated carcinomas or melanomas (thiopyrylium salts: 88USP4774250), and fluorescent biological stains (thiopyrylium salts: 84JAP59133460). Thio-, seleno-, and, especially, telluropirylium dyes hold promise as photosensitizers for photodynamic therapy, a recently developed technique for the treatment of cancer (88JA5920; 89EUP315491, 89MI3, 89MI4; 90JA3845, 90JAP02-164825, 90JMC1108, 90MI4; 91MI5).

Thiopyrylium salts can find application in analytical chemistry. Thus, 2,4,6-triphenylthiopyrylium chloride can be used as a precipitant for the quantitative gravimetric determination of anions (ClO_4^- , ClO_3^- , NO_3^- , BF_4^-) (87MI3). Thiopyrylium salts can be also used in the spectrophotometric determination of bismuth (75URP482648), tellurium (77URP-558856), palladium (77URP558865), and alkyl sulfates (91URP1675746).

Other sparse applications include the use of thiopyrylium salts for the preparation of optically nonlinear organic media (86CPL209), for the preparation of nonaqueous electrolytes for electrolytic capacitors (87JAP62-200718), and for dyeing of acrylic (88MI8) and polyamide fibers (76URP508518) and the use of telluropirylium salts in eyeglasses for eye protection against laser beam exposure (88JAP63-68161).

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Heterocyclic Betaines: Pyridinium (Imidazolium) Azolate Inner Salts with Several Interannular Linkages¹

ERMITAS ALCALDE

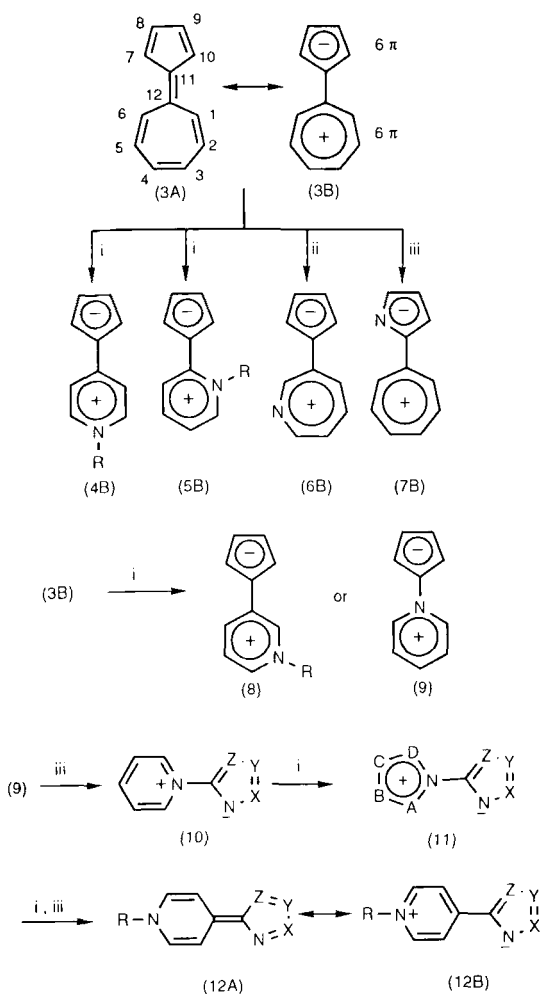
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¹ Dedicated to Professor José Elguero

SCHEME 1.

a nitrogen atom, i.e., **6**; (iii) to replace a carbon atom of the cyclopentadiene by a nitrogen atom, i.e., **7**. Compound **3** and its heteroanalogues (i.e., **4–7**) are cyclic cross-conjugated π -bond systems, which can be described to a first approximation by a covalent resonance structure and a dipolar one; Scheme 2 shows structures **4–7** represented in their dipolar resonance form **B**. The first possibility has been carefully explored, and the term heteroanalogues of sesquifulvalene is normally used for those that are



SCHEME 2. Aza analogues of sesquifulvalene (**3**): (i), $\text{>C}=\text{C}< \rightarrow \text{-NR-}$; (ii, iii) $\text{>C}=\text{C}< \rightarrow \text{>C}=\text{N-}$, (91JOC4223). X, Y, Z, A, B, C, D: =CR-, =N-.

derived formally from **3** by replacement of the seven-membered carbocyclic ring by a quaternary heteroaromatic ring [69AG(E)478; 74HC(1)309, 74HC(2)378; 85M11]. To our knowledge, the second and the third possibilities have not been reported.

Within the first possibility, it is of interest to consider structures **8** and the *N*-ylide **9** in which the covalent resonance form is forbidden. They may exist only as betaines, being aza analogues of the dipolar form of sesquifulvalene (**3B**). *N*-Pyridinium cyclopentadienide **9** is a typical example of conjugated heterocyclic *N*-ylides isoconjugated with odd nonalternant hydrocarbon anions (85T2239). The azinium azolate **10** and azolium azolate **11** inner salts are aza analogues of the *N*-ylide **9** and belong to this class of mesomeric heterocyclic betaines. The aza analogues of sesquifulvalene **12** are an example in which possibilities i and iii are combined. These push-pull ethylenes should show a spectrum of properties ranging between those of ethylenes and betaines.

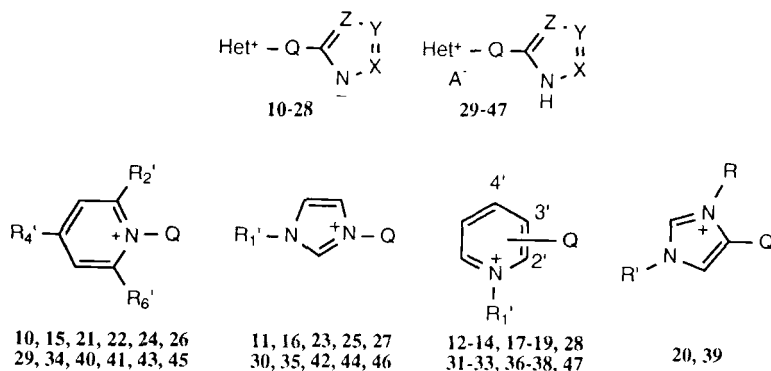
A. SCOPE

Heterocyclic betaines and other unusual structures have been the subject of extensive investigation [88AHC(44)269; 92AHC32]. The specific focus of this report is to survey recent progress in the chemistry of heterocyclic betaines and molecules with a betaine character of general type **1** (Scheme 1), and should serve to complement other reviews that deal with heterocyclic betaines of alternant hydrocarbons [80AHC(26)1] and heterocyclic mesomeric betaines (85T2239).

Compounds of general structure **1** contain extremely π -deficient and π -excessive heteroaromatic moieties linked with several spacers: from aza analogues of sesquifulvalene **10–14** to their vinylogues **15–21** and related systems **22–28** (Scheme 3 and Table I).

Structures of type **15** to **20** can also be considered aza analogues of (*E*)-stilbene; compounds **17** and **18** are an unusual type of push-pull (*E*)-stilbene that should show a spectrum of properties ranging between those of (*E*)-stilbenes and betaines. The 19 types of compounds selected, **10–28**, and their precursors, **29–47**, outlined in Scheme 3 and Table I, have been ordered by: (a) the nature of the interannular linkage (-Q-); (b) the nature of the two atoms linking the π -deficient nucleus and the interannular group (C—N' bond type and C—C' bond type); (c) the substitution pattern between the π -deficient nucleus and the interannular group.

This chapter contains data on compound pairs of types **10–28** and **29–47** (Scheme 3 and Table I). The literature available to the author has been covered up to December 1992.



SCHEME 3. Compound pairs **10–28** and **29–47** (see Table I). Structures of type **12**, **13**, **17** and **18** are represented in their dipolar resonance form.

TABLE I
PYRIDINIUM (IMIDAZOLIUM) AZOLATE INNER SALTS (**10**)–(**28**) WITH SEVERAL
INTERANNULAR SPACERS, AND THEIR IMMEDIATE PRECURSORS (**29**)–(**47**)^a

-Q-	Het ⁺ -Q bond type	
	C—N' bond	C—C' bond
Q:—	10^b, 29	11^b, 30
12 4-(azolylidene)-1,4-dihydropyridines		12^b, 31
13 2-(azolylidene)-1,2-dihydropyridines		13^{b,c}, 32^c
14 (1-alkyl-3-pyridinio)		14, 33 (c)
Q: (E)—CH=CH—	15^d, 34	16^d, 35
17 4-[2-(azolylidene)ethylidene-1,4-dihydropyridines]		17, 36
18 2-[2-(azolylidene)ethylidene-1,2-dihydropyridines]		18, 37
19 [2-(1-alkyl-3-pyridinio)vinyl]		19, 38
20 [2-(1,3-dialkylimidazolio)vinyl]		20, 39
Q: <i>p</i> -phenylene	21, 40	(c) (c) (c)
Q: —(CH ₂) _n —		
<i>n</i> = 1	22, 41	23, 42 (e) (c)
<i>n</i> = 2	24, 43	25, 44 28^d, 47 (c)
		(4-pyridinio)
<i>n</i> = 5	26, 45	27, 46 (c) (c)

^a See Scheme 3.

^b See Scheme 2.

^c These series have yet to be studied.

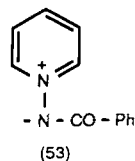
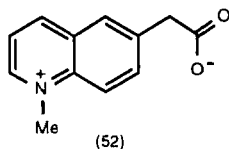
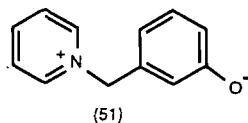
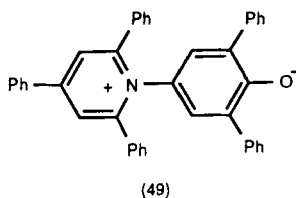
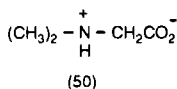
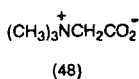
^d These series have only been studied by semiempirical methods.

^e See II,A,1 and IV,D.

B. NOMENCLATURE

The trivial name betaine corresponds to the natural dipolar ion **48** and serves as the generic term for a variety of natural and synthetic compounds with positive and negative centers within a single structure (79MI1; 87MI1). A prime example is pyridinium *N*-phenolate betaine, Reichardt's dye **49**, which exhibits one of the largest solvatochromic effects ever observed, and is a new type of solvent polarity indicator (88MI1; 92CSR147).

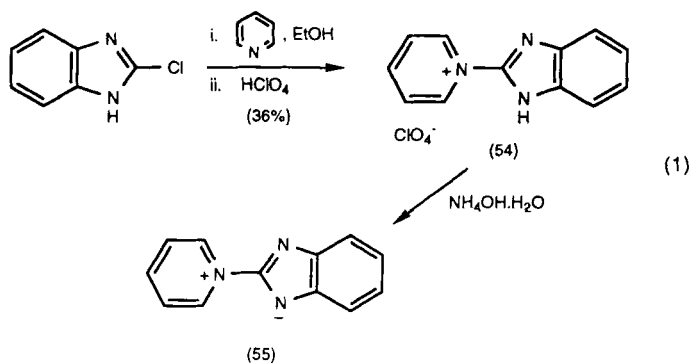
The nomenclature of dipolar ions is varied, probably due to semantic assimilation of betaine, i.e., **48**, and zwitterion, i.e., **50** (79MI1). A casual terminology for dipolar ions proposed by Nickon and Silversmith (87MI1) has clarified their denomination. Furthermore, Ollis *et al.* (85T2239) have proposed a new classification and nomenclature for heterocyclic mesomeric betaines that emphasizes the isoconjugated relation of 16 classes of heterocyclic mesomeric betaines to alternant and nonalternant hydrocarbon anions and dianions. Moreover, the recommended designation of dipolar ions exemplified by compounds **51** and **52** is zwitterions due to the fact that the positive and negative charges are specifically associated with separated π -electron systems (85T2239). Among other dipolar ions, the heteroaromatic *N*-imines **53**, perhaps better referred to as *N*-ylides, are an example in which several denominations coexist [81AHC(29)71].



II. Synthesis

In 1966, Boyd reported the synthesis and properties of 2-(1-pyridinio)-benzimidazolate **55**, a stable aza analogue of pyridinium cyclopentadienide **9** (66TL3369). With this, a novel type of heterocyclic mesomeric betaine was found.

The bright yellow crystalline *N*-ylide **55** was prepared by a two-step procedure as illustrate in Eq. (1). New compounds were described in this category **10** (see Table I) by Röchling *et al.* [70ZN(B)954] and Postovskii *et al.* (75KGS987). However, the chemistry of these *N*-ylides was not explored until some time later (86CC734; 87JOC5009; 88TH1; 90M13).



Methods of synthesis leading to pyridinium (imidazolium) azolate inner salts and related compounds with a betaine character **1** can be varied. In almost all cases, their protonated compounds azolypyridinium (imidazolium) salts with several interannular linkages **2** are useful as synthetic intermediates (Scheme 1). These quaternary salts of nitrogen heteroaromatic compounds **2** allow us to deepen the study of classical reactions and seek suitable alternatives for their preparation.

Thus, compounds **2** are interesting substrates with which to study either classical Phillips synthesis (91JOC6516; 92CL2357; 93CPB614) or Hein's benzimidazole synthesis (91JOC6516; 92CL2357, 92S395, 92UP1; 93CPB614) as well as a Knoevenagel-type condensation (91CL2151; 92JOC4834, 92TH1). Going further, selected prototype structures **2** may be attractive substrates for seeking further insight into fundamental topics in both organic and heteroaromatic chemistry, for instance, (a) the use of quaternary heteroaromatic substrates as leaving groups [84AG(E)420, 84CSR47; 88AHC(43)173; 90CSR83, 90JA2471, 90JA8878] and (b) application of the Kauffmann's areno-analogy principle [79AG(E)1], which relates heteroaromatic fragments with classical functional groups (77H911; 88TH1; 91JOC4223, 91TH1; 92TH1).

A. AZOLYLPYRIDINIUM (IMIDAZOLIUM) SALTS

There are several methods for obtaining azolypyridinium and azolyliimidazolium salts **29–33** and their vinylogues **34–40** and homologues **41–47**

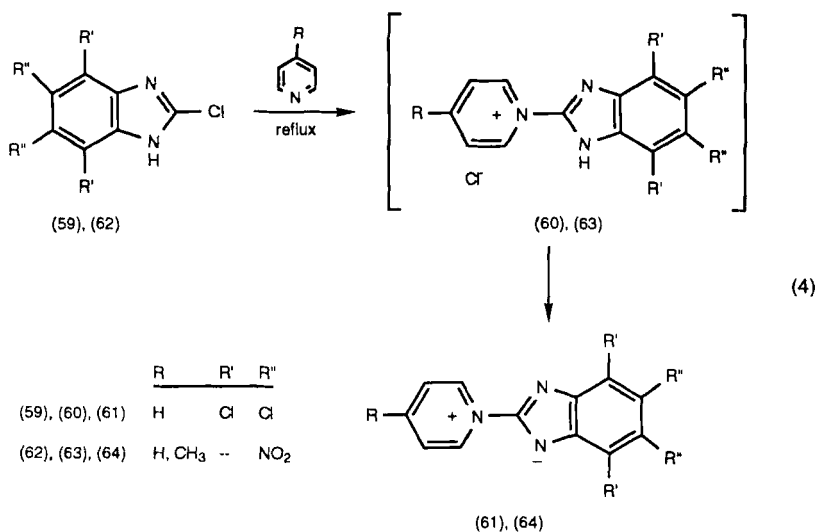
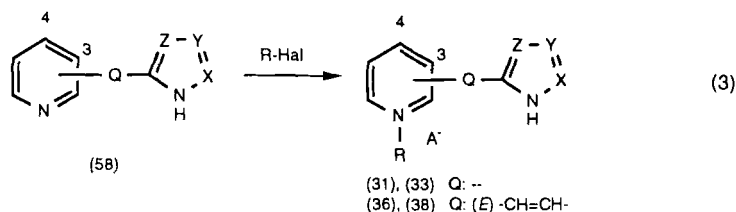
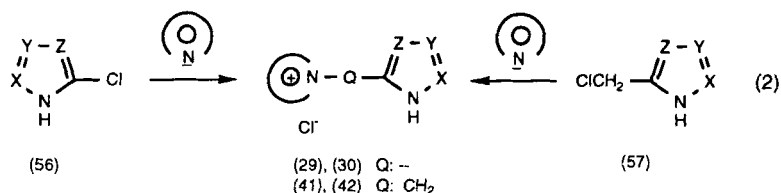
SCHEME 4.

TABLE II
AZOLYLPYRIDINIUM (IMIDAZOLIUM) SALTS (29), (30), (31), (33), THEIR VINYLOGUES (36),
AND (38), AND HOMOLOGUES (41), (42), OBTAINED BY NUCLEOPHILIC
SUBSTITUTION REACTIONS^a

Structure	Q	Azolyl	Method ^b	Reference(s)
(29)	—	1 <i>H</i> -Benzimidazol-2-yl	A	66TL3369; 70ZN(B)954; 75KGS987; 86CC734; 87JOC5009; 88TH1; 90MI3; 91TH1; 92MI3
(29)	—	1 <i>H</i> -Benzimidazol-2-yl	B	86EUP181846, 86JMC1327; 87JOC4573, 87JOC5009; 90JOC4163
(30)	—	1 <i>H</i> -Benzimidazol-2-yl	A	88TH1, 88TL491; 91JOC4233, 91TH1; 92MI3
(30)	—	1 <i>H</i> -1,2,4-Triazol-3(5)-yl	A	88TH1, 88TL491; 91JOC4233
(31)	—	1 <i>H</i> -Benzimidazol-2-yl	C	77H911; 79JHC1583; 88TH1; 89CC1086; 91JOC4223, 91TH1
(31)	—	1 <i>H</i> -Pyrazol-3-yl	C	68JMC981; 88TH1; 89CC1086; 91JOC4223
(31)	—	1 <i>H</i> -1,2,4-Triazol-3(5)-yl	C	69JMC944
(31)	—	1 <i>H</i> -Indol-3-yl	C	70JMC993; 78KGS1481
(31)	—	1 <i>H</i> -Pyrrol-3-yl	C	71JMC214
(31)	—	1 <i>H</i> -Tetrazol-5-yl	C	69JMC944
(31)	—	1 <i>H</i> -Imidazol-2-yl	C	69JMC944
(33)	—	1 <i>H</i> -Benzimidazol-2-yl	C	79JHC1579
(33)	—	1 <i>H</i> -Tetrazol-5-yl	C	82JCR(S)122
(36), (38)	(E)—CH=CH—	1 <i>H</i> -Benzimidazol-2-yl	C	91CL2151; 92MI4, 92TH1; 93CPB614
(41)	—CH ₂ —	1 <i>H</i> -Benzimidazol-2-yl	C	88H1233; 89H57; 90T6033; 91CL845, 91TH1; 92JOC4829
(41)	—CH ₂ —	1 <i>H</i> -1,2,4-Triazol-3(5)-yl	C	91CL845, 91TH1; 92JOC4829
(41)	—CH ₂ —	1 <i>H</i> -Pyrazol-3(5)-yl	C	91TH1
(42)	—CH ₂ —	1 <i>H</i> -Benzimidazol-2-yl	C	91CL845, 91TH1; 92JOC4829
(42)	—CH ₂ —	1 <i>H</i> -1,2,4-Triazol-3(5)-yl	C	91CL845, 91TH1; 92JOC4829
(42)	—CH ₂ —	1 <i>H</i> -Pyrazol-3(5)-yl	C	91TH1

^a See Scheme 4.

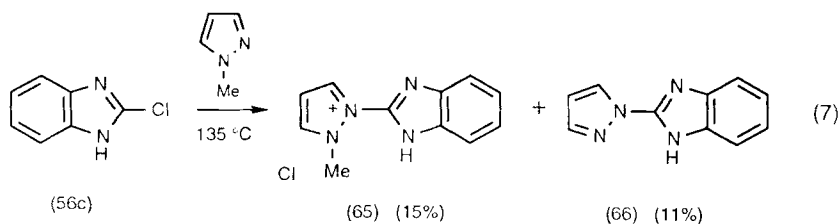
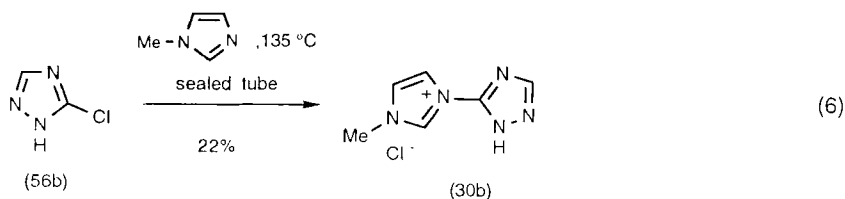
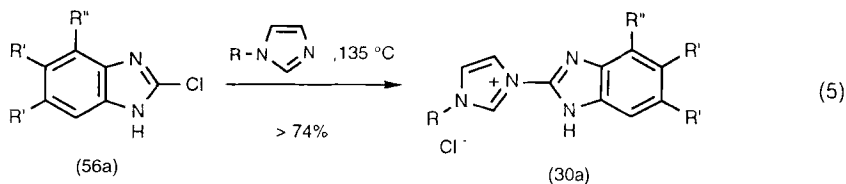
^b Method A, S_N Ar; Method B, Smiles rearrangement; Method C, Menshutkin-type reaction.



promoted the formation of *N*-ylides **61** and **64** from their corresponding *N*-benzimidazolypyridinium salts **60** and **63**, owing to the intrinsic acidity of the polysubstituted benzimidazole nucleus with not only a 2-(1-pyridinio) group but also chloro or nitro groups in the benzenic moiety. For instance, the pK_a (proton lost) of benzimidazole itself is 12.86, whereas for 2-nitrobenzimidazole it is 6.9 and for 5,6-dinitrobenzimidazole it is 10.7 (87AHC187).

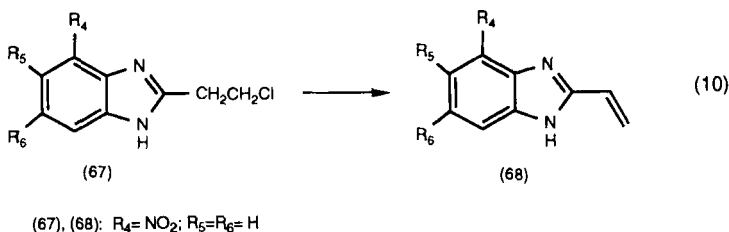
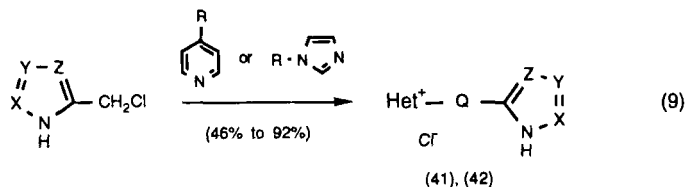
This route has been applied for the preparation of several *N*-benzimidazolypyridinium(imidazolium) salts **29** and **30** (see Table II), as well as other azolium salts **30** (88TH1; 91JOC4233, 91TH1). The scope of the

S_NAr method is limited to activated halogenoazoles, as is the case of 2-chlorobenzimidazoles **56a** or to a lesser extent 3(5)-chloro-1,2,4-triazoles **56b** (91JOC4233) [Eq. (5) and (6)]. The reaction temperature is of crucial importance to avoid, as far as possible, the undesired dealkylation by-products (91JOC4233) [Eq.(7) and (8)].

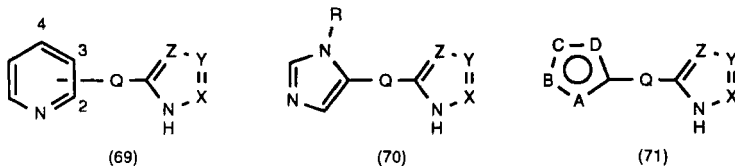


The most usual way to obtain quaternary aza-heteroaromatic salts is a subclass of the Menshutkin reaction. This is a typical S_N2 reaction, but apart the mechanism of nucleophilic substitution at a saturated carbon atom [88AHC(43)173; 90CSR83; 91JOC5039], the reaction involves a tertiary amine and an alkylating agent. In this connection, quaternization of aza-aromatic compounds (e.g., pyridines) has been the subject of extensive research [64AHC1; 74HC(1)309; 78AHC71; 79AJC1735; 81AJC163, 81AJC2569; 84MI1; 88AHC(43)173].

The (azolylmethyl)pyridinium and imidazolium salts **41**, **42** were obtained by reaction of chloromethylazoles with a pyridine or a 1-alkylimidazole (92JOC4829) [Eq.(9)]. For the higher homologues, the starting 2-chloroethylazoles are not suitable intermediates, owing to their intrinsic instability, even in the solid state. For instance, 2-(2-chloroethyl)-4-nitrobenzimidazole **67** was easily transformed to the corresponding 2-vinyl-4-nitrobenzimidazole **68**, along with transformation or decomposition products (91JOC6516) [Eq.(10), IV,C].



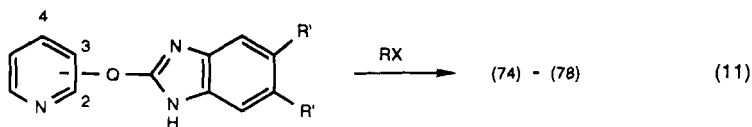
However, quaternizing more complex molecules of type **69–71** might give a mixture of products, and deserves brief comment. These compounds provide an attractive basic set for the study of reactions with an alkylating agent under neutral conditions (Menschutkin reaction conditions). There are at least three annular nitrogen *sp*² atoms to which an alkylating agent may be delivered: (i) *N*-alkylation of the π -excessive azole nucleus (84M12) and quaternization of the pyridine-like nitrogen atoms contained in (ii) the π -deficient ring (i.e., pyridine) and (iii) the π -excessive ring (i.e., 1-azolazole).



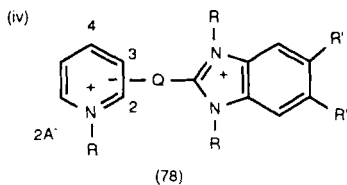
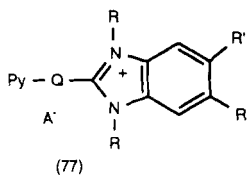
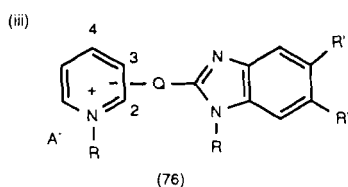
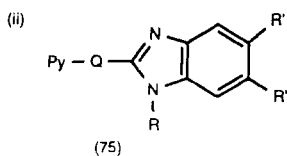
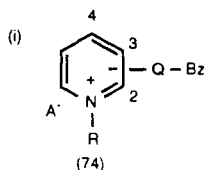
X, Y, Z, A, B, C, D: =CR-, =N-

The 2-(pyridyl)-1*H*-benzimidazoles **72** and their vinylogues **73** can serve as models and might lead to the formation of five alkylated derivatives

74–78 [Eq.(11)]. Depending on the pK_a of the π -excessive ring (87AHC187), compounds of type **74–76** may be obtained either as free bases, as in Eq.(9), or as their conjugated acid species. Moreover, if the benzimidazole nucleus were unsymmetrically substituted in **75** and **76**, the formation of their corresponding regioisomers could be expected.



(72) Q: --
 (73) Q: (E) -CH=CH-

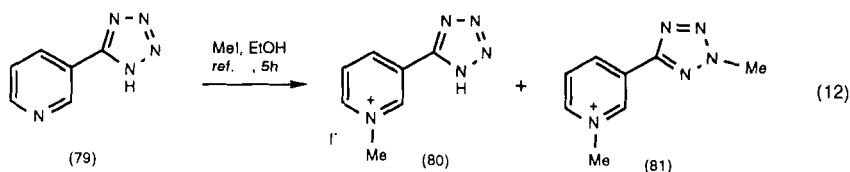


Quaternizing the pyridine ring leads to the target compounds **74**, which are examples of the pyridinium salts **31**, **33** and their vinylogues **36**, **38** [see Eq.(3) and Table II].

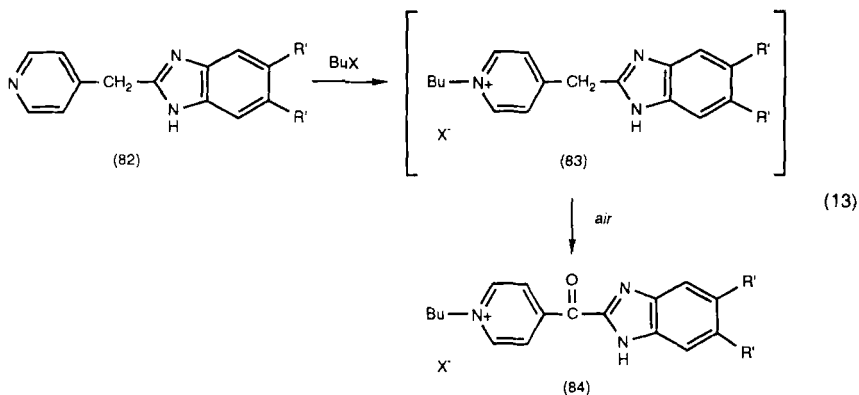
The benzimidazole derivatives **72** and **73** have been studied, and to a lesser extent other azole derivatives of general type **69**. When the starting material contains a pyridine ring substituted in the 4- or 3- position, quaternization of this ring is usually favored, giving the target pyridinium salts **74** as the major products in fairly good yield (i.e., **31**, **36** and **33**, **38**, Table II).

In contrast, with a 2-substituted pyridine moiety, the selectivity of alkylation tends toward the π -excessive ring and compounds of type **75** and/or **77** may be found. Therefore, this route is not advisable for the synthesis of the pyridinium salts of type **32** and **37** (Section II,A,3). In fact, the steric and electronic interference in quaternization has an important role in *ortho*-substituted pyridine systems [88AHC(43)173].

Barni *et al.* (79JHC1579, 79JHC1583; 84JHC561) have studied the reaction of 2-(pyridyl)-1*H*-benzimidazoles **72** with methyl iodide in neutral conditions. Other (4-pyridyl)-1*H*-azole systems have been used for the preparation of their corresponding pyridinium salts of type **31** (Table II). Concerning 3-pyridinio and 2-pyridinio derivatives **33**, **34**, Butler and Garvin [82JCR(S)122] have reported the methylation of 5-(3-pyridyl)tetrazole **79**, giving the pyridinium compounds **80** and **81** [Eq.(12)] [Section II,B,2, Eq.(26)].



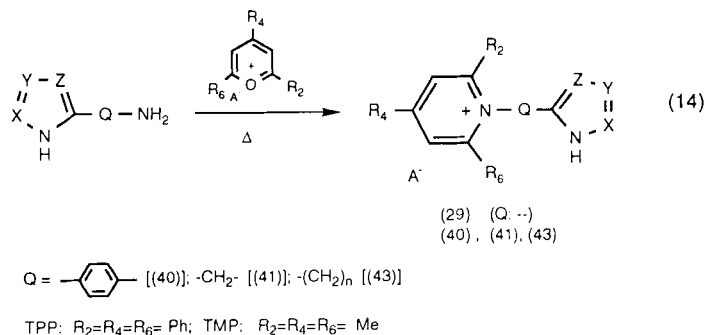
The behavior of 2-(pyridylvinyl)-1*H*-benzimidazoles **73** toward neutral alkylation has been studied (91CL2151; 92TH1, 92UP1). Starting from 2-(4-pyridylvinyl) and 2-(3-pyridylvinyl) intermediates, the pyridinium salts of type **74** were obtained as the major products, whereas for the 2-(2-pyridylvinyl) intermediate the high selectivity of alkylation led to a single product, the conjugated acid of the 1-alkyl-2-substituted benzimidazole counterpart **75** [see Eq.(11)].



Quaternizing the heteroarylmethanes of type **82**, homologues of the above-mentioned structure type **72**, with iodobutane or bromobutane gave the 1-alkyl-4-(benzimidazol-2-ylmethyl)pyridinium salts **83**, which underwent spontaneous oxidation to their oxomethyl analogues **84** (91TH1) [Eq.(13),IV,D,Eq. (43)]. This unprecedented chemical behavior of a carbon atom linked to nonclassical acceptor and donor functional groups of compounds of type **83** exemplifies a concurrent application of captodative effect (85ACR148; 88PAC1635) and Kauffmann's areno-analogy principle [79AG(E)1].

2. From Pyrylium Salts

Among the variety of pyrylium salt ring transformations, their reaction with primary amines to give 1-substituted pyridinium salts is a well-known procedure [74HC(1)309; 82MI1]. It is an alternative and complementary synthetic route to the quaternization of pyridines by the Menshutkin-type reaction (Section II,A,1). However, only a few examples of *N*-heteroaryl-substituted pyridinium salts **29** from *C*-aminoazoles have been reported together with their homologues **41**, **43** and vinylogues **40** (82MI1; 87JOC5009) [Eq. (14)]. In the useful review of Balaban *et al.* (82MI2) there are several references to *N*-substituted pyridinium salts obtained from pyrylium salts more or less related to compound types **29**, **41**, and **43**. These have mostly been omitted in Table III unless there is any other report related to the subject.



Using this route, several examples of *N*-(benzimidazol-2-yl)pyridinium salts with a 2,4,6-triphenylpyridinium group **85** (87JOC5009; 90MI39; 91MI4; 92MI3) or a 2,4,6-trimethylpyridinium group **86** (90MI3) and their vinylogues **87** (87JOC5009) and **88** (90MI3) have been reported, and their biological properties have also been examined (V).

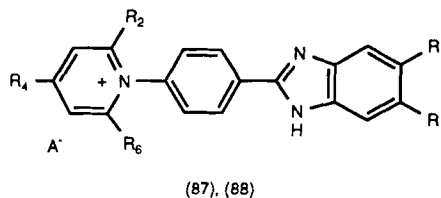
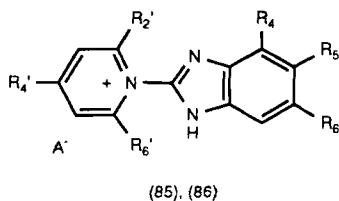
TABLE III
AZOLYLPYRIDINIUM (IMIDAZOLIUM) SALTS (29) AND THEIR VINYLOGUES (40) AND
HOMOLOGUES (41), (43), OBTAINED FROM PYRYLIUM SALTS^a

Structure	Q	Azolyl	R-2', 4', 6'	Reference(s)
(29)	—	1 <i>H</i> -Benzimidazol-2-yl	TPP	74KGS1461; 75KGS1180; 78KGS944; 86CC734; 87JOC5009; 88TH1; 90MI3, 91MI4; 92MI3
(29)	—	1 <i>H</i> -Benzimidazol-2-yl	TMP	80RRC1505; 88TH1; 92MI3
(29)	—	1 <i>H</i> -Pyrazol-3-yl	TPP	86CC734; 87JOC5009; 88TH1
(29)	—	1 <i>H</i> -Pyrazol-3-yl	TMP	88TH1; 90MI3
(29)	—	1 <i>H</i> -1,2,4-Triazol-3(5)-yl	TPP	74KGS1461; 78KGS944; 86CC734; 87JOC5009
(29)		3(5)-Amino-1 <i>H</i> -1,2,4- triazol-5(3)-yl	TPP	87JOC5009
(29)		1 <i>H</i> -Tetrazol-5-yl	TPP	74KGS1461; 78KGS944; 86CC734; 87JOC5009
(40)	<i>b</i>	1 <i>H</i> -Benzimidazol-2-yl	TPP	87JOC5009; 88TH1
(40)	<i>b</i>	1 <i>H</i> -Benzimidazol-2-yl	TMP	88TH1; 90MI3
(41) ^c	—CH ₂ —	1 <i>H</i> -Benzimidazol-2-yl	TPP	70KGS315; 73KGS1682
(41) ^c	—CH ₂ —	1 <i>H</i> -Benzimidazol-2-yl	TMP	70KGS315; 73KGS1682
(43) ^c	—(CH ₂) ₂ —	1 <i>H</i> -Benzimidazol-2-yl	TPP	73KGS1682; 74KGS1461; 78KGS944
(43) ^c	—(CH ₂) ₂ —	1 <i>H</i> -Benzimidazol-2-yl	TMP	73KGS1682

^a See Eq. (14).

^b *p*-Phenylene.

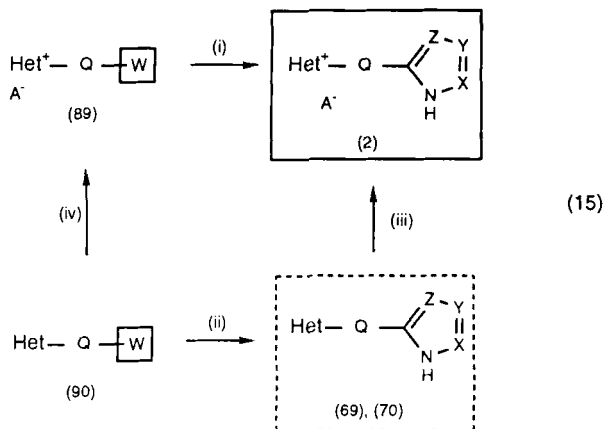
^c For examples with different azolyl moiety, see Balaban *et al.* (82MI2).



(85), (87) R₂'=R₄'=R₆'=Ph; (86), (88) R₂'=R₄'=R₆'=Me

3. *By Generation of the Azole Nucleus in the Last Synthetic Step*

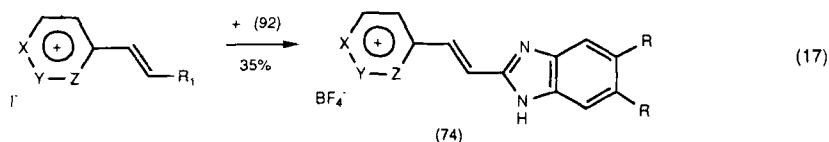
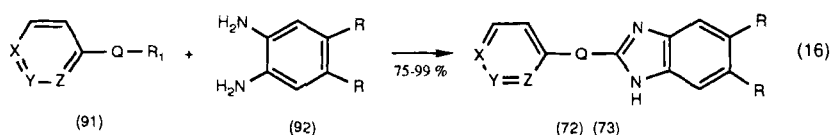
The most attractive route of the target quaternary heteroaromatic salts **2** appears to be the formation of the π -excessive moiety from conveniently functionalized pyridinium or imidazolium intermediates **89** [Eq.(15)], and this should be studied in detail for each case. For this purpose existing methods for the synthesis of azoles can be adapted as long as the selected procedure is performed in neutral or, better, in acidic media, owing to the presence of a cationic moiety in the key intermediate **89**.



Alternatively, the uncharged intermediate of type **90** can be transformed to a wide range of uncharged compounds **69**, **70**, which in turn may be selectively quaternized, always bearing in mind the polyalkylation drawback [Section II,A,1 and Eq.(11)]. Thus, the limiting factors of the procedures shown in Eq.(15) are as follows: for transformation (i) the reaction has to be carried out in neutral or acidic media and at temperatures below 160°C, whereas for (iii) the neutral alkylation with an alkyl halide may be selective.

Probably the best method for synthesizing 2-substituted benzimidazoles makes use of the cyclodehydration reaction between a carboxylic acid or derivative and 1,2-arylenediamines under acidic conditions (81HC6). Both 2-(pyridyl)-1*H*-benzimidazoles **72**, **73** and 1-alkyl-(1*H*-benzimidazol-2-yl)pyridinium salts **74** shown in Eq.(11) have been efficiently synthesized by Hein's benzimidazole synthesis (92S395, 92UP1; 93CPB614) [Eq.(16) and (17)].

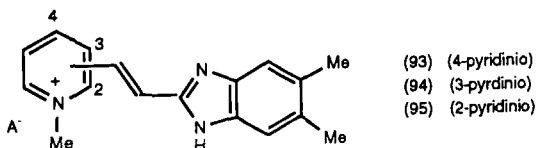
The (azolyethyl)pyridinium salts **43** have been obtained by two alternative procedures that have sufficient flexibility to allow conveniently substi-



tuted benzimidazoles to be generated from a variety of *o*-arylenediamines (91JOC6516) [Eq.(18) and (19)]. Both approaches have also been applied for synthesis of azolyethylimidazolium salts **44** (92CL2357, 92MI2).

Several quaternary salts of type **39**, **43–46** have been prepared either by Hein's benzimidazole synthesis [see Eqs.(17) and (18)] or using an acylchloride, instead of the carboxylic acid or derivative, as shown in Eq.(19) (Table IV).

The general synthetic scheme of Eq.(15) has been applied to the three isomers of 1-methyl-(benzimidazolylvinyl)pyridinium salts **93–95**, which are examples of compounds of type **74** mentioned in Section II,A,1 [see Eq.(11)] and in Eq.(17). Synthesis of the 4-pyridinio and 3-pyridinio derivatives **93**, **94** can be achieved either via (i) from Eq.(15) [(92S395), Eq.(17)] or via (ii) and (iii) [(91CL2151; 92UP1), Eq.(11)]. A different situation holds for the 2-pyridinio compound **95**, which was only prepared by via (i) owing to the steric and electronic interference to quaternization of *ortho*-substitute pyridine compounds (92UP1) [Eq.(11), Section II,A,1].



Syntheses of various types of quaternary salts **2** containing a 2-benzimidazole ring are summarized in Table IV; the best results have been achieved using the modified protocol of Hein's benzimidazole synthesis.

Alvarez-Builla and co-workers synthesized several examples of *N*-benzimidazolylmethylpyridinium salts of type **41** by cyclization of new dithioesters with 1,2-arylenediamines **92** (88H1233; 89H57) [Eq.(20)], in the course of an investigation on the chemistry of dithioesters and highly stabilized ylides (90T6033). For other examples of pyridinium salts **41** see Tables II and III.

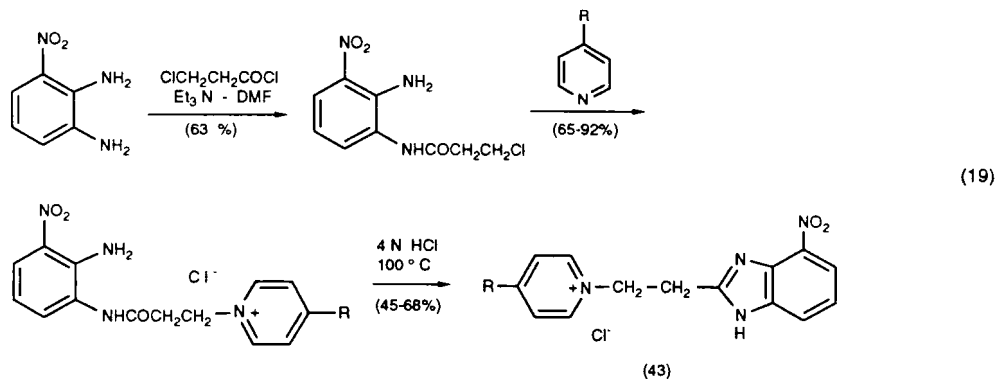
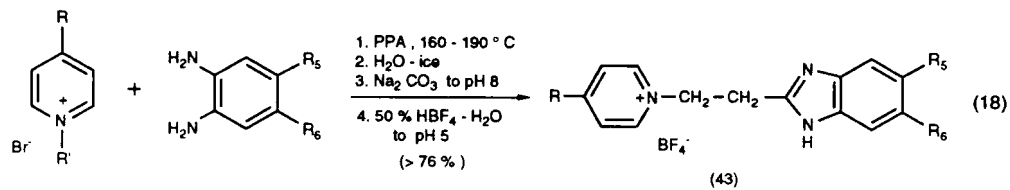
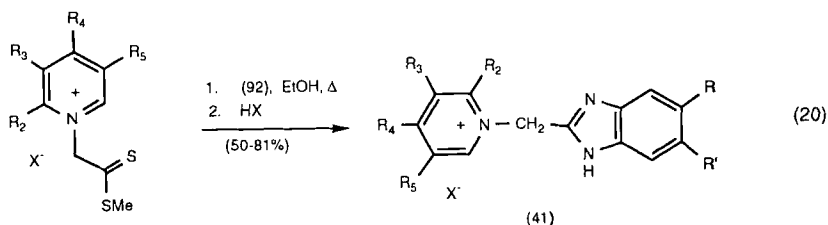


TABLE IV
(1*H*-BENZIMIDAZOL-2-YL)PYRIDINIUM (IMIDAZOLIUM) SALTS WITH VARIOUS
INTERANNULAR SPACERS OBTAINED BY GENERATION THE 2-SUBSTITUTED
BENZIMIDAZOLE NUCLEUS IN THE LAST SYNTHETIC STEP

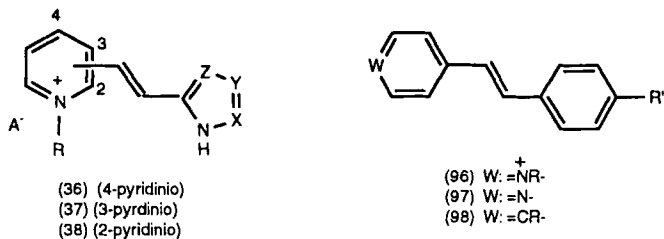
Structure ^a	Spacer		Reference(s)
	C—Q—C'	C—Q—N'	
(36)–(38)	(<i>E</i>)—CH=CH—		92S395, 92TH1
(39)	(<i>E</i>)—CH=CH—		92CL1779, 92TH1
(41)		—CH ₂ —	88H1233; 89H57, 90T6033
(43)		—(CH ₂) ₂ —	76JCS(P1)312; 91JOC6516, 91TH1
(44)		—(CH ₂) ₂ —	92CL2357, 92M12
(45), (46)		—(CH ₂) ₅ —	92UP2

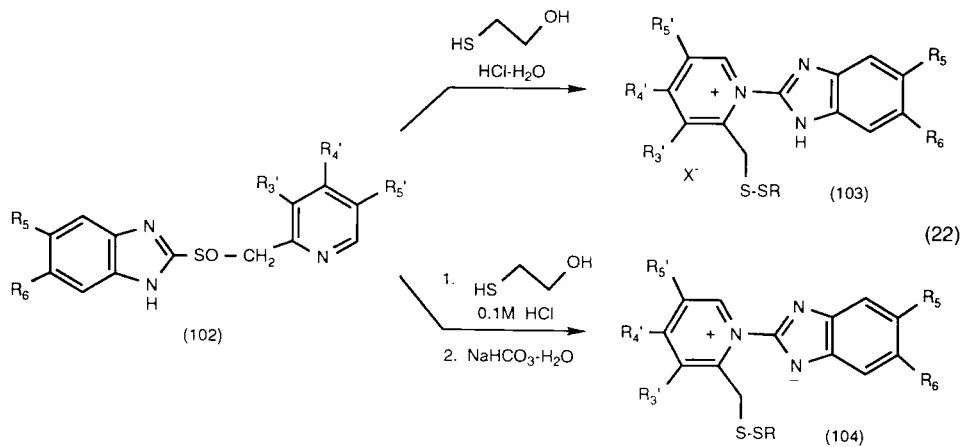
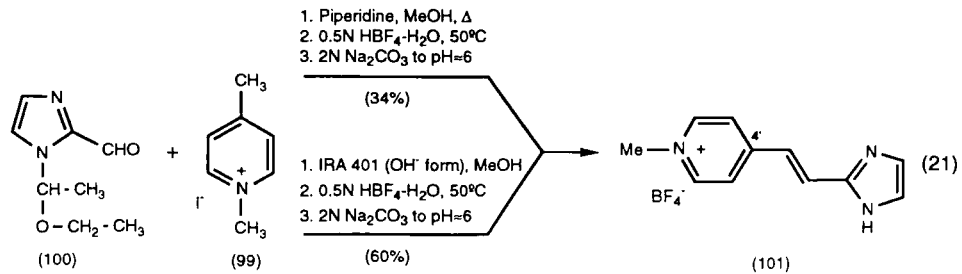
^a See Table I.



4. Condensation Reactions

The extended π -systems constituted by the ensemble of the quaternary heteroaromatic salts of type **36–38** could theoretically be prepared using existing condensation reactions for the synthesis of (*E*)-stilbazolium salts **96**, (*E*)-stilbazoles **97**, and (*E*)-stilbenes **98**. Among these, a widely used procedure, the Knoevenagel condensation (67OR204; 86ACR121), was applied for the preparation of (*E*)-imidazolylvinylpyridinium salt **101** (91CL2151; 92JOC4834) [Eq.(21)]. An improved protocol for a





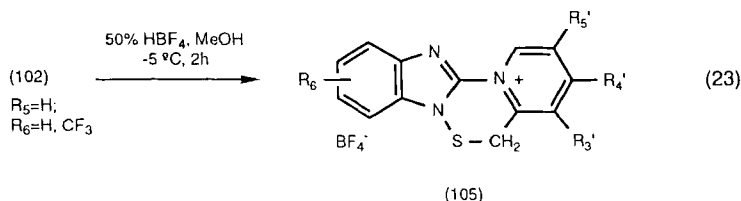
Knoevenagel-type condensation using a strongly basic ion-exchange resin provides a simple entry into a variety of (*E*)-imidazolylvinylpyridinium salts of type **36** and **37**; for instance, compound **101** was obtained in good yield by this type of reaction (91CL2151; 92JOC4834, 92TH1) [Eq.(21)]. In the same way, an indolylvinylpyridinium tetrafluoroborate has been prepared (92MI4) (III,D, Scheme 10).

Regarding Knoevenagel condensation, a wide range of aromatic aldehydes are known and easily accessible. However, the less common azolecarbaldehydes are difficult to obtain (i.e., 2-imidazolecarbaldehydes), and this could prove to be a limiting factor for the method. Moreover, the starting picolinium salt has to contain the C₂-Me or C₄-Me side chain (i.e., compound **99**). This approach is not useful for the preparation of 3-substituted pyridinium salts **38**, and other methods must be used for this purpose [74HC(1)309; 92TH1].

5. Miscellaneous Reactions

Other methods may be applied to obtain specific pyridinium salts of general type **2** and they could be complementary to the more general procedures reported above (II,A,1 to 4).

Sulfoxides **102** (PSB_S) (90M11), through a proposed acid catalyzed pathway, have been transformed to some types of compounds containing quaternary pyridinium moieties. Among them, several *N*-benzimidazolylpyridinium salts **103** (86EUP181846, 86JMC1327) or their mesomeric betaines **104** (86CC125; 87JOC4573) [Eq.(22)] together with several dimeric compounds (90JOC4163) have been reported. Protonation of **102** produces a consecutive-cascade of transformations that are highly dependent on the conditions applied, and it has been possible to isolate a few cyclic sulfenamide intermediates **105** generated by a type of intramolecular S_N, Smiles rearrangement, of sulfoxides (87JOC4582) [Eq.(23)]. The compound pairs **103** and **104** are examples of the pyridinium salts **29** (see Tables II and III) and mesomeric heterocyclic betaines **10** (see Section II,B and Table V), respectively.



For the preparation of azolylpyridinium salts of general type **2**, neither of the well-known Zincke-König reactions [74HC(1)309; 81T3423] or the

TABLE V
PYRIDINIUM (IMIDAZOLIUM) AZOLATE BETAINES AND COMPOUNDS WITH A BETAINE
CHARACTER **10-27** OBTAINED FROM THE CORRESPONDING QUATERNARY
HETEROAROMATIC SALTS **29-46**

Structure ^a	Compound	Basic medium	Yield (%)	Reference(s)
(10)	(55) ^b	NH ₄ OH-H ₂ O	99	66TL3369; 87JOC5009
(10)	(61) ^c	Pyridine	38	70ZN(B)954
(10)	(64) ^c	Pyridines	99	75KGS987
(10)	(104) ^d	NaHCO ₃ -H ₂ O	>32	87JOC4573
(10)	(104) ^d	NaHCO ₃ -H ₂ O	73	87JOC4582
(10)	(149) ^{e,f}	KOH-EtOH	96	78KGS944
(10)	(149) ^{e,f}	Anion-exchange resin	96	87JOC5009
(10)	(149) ^{e,g}	H ₂ O	88	78KGS944
(10)	(149) ^{e,g}	Anion-exchange resin	90	87JOC5009
(10)	(149) ^e	Anion-exchange resin	>90	87JOC5009; 90MI3; 91MI4; 92MI3
(10) ^h		NH ₄ OH-H ₂ O or K ₂ CO ₃ -H ₂ O	>91	92MI3
(11)		Anion-exchange resin	>90	91JOC4233
(11)		K ₂ CO ₃ -EtOH-H ₂ O	>80	91JOC4233
(11) ^h		NH ₄ OH-H ₂ O or K ₂ CO ₃ -H ₂ O	>80	92MI3
(12)		Anion-exchange resin	>95	91JOC4223
(12)	(115) ⁱ	KOH-EtOH-H ₂ O	>91	78KGS1481
(14)	(109) ^j	Et ₃ N-DMSO	17	82JCR(S)122
(17)-(19)		Anion-exchange resin	>83	91CL2151; 92UP1; 93CPB614
(17), (18)		Anion-exchange resin	>82	91CL2151; 92JOC4834
(20)		Anion-exchange resin	>94	92CL1779, 92TH1
(21)		Anion-exchange resin	>96	87JOC5009; 90MI3
(22), (23)		Anion-exchange resin	>81	91CL845, 91TH1; 92JOC4829
(24) ^h		Anion-exchange resin	95	92MI2
(25)		Anion-exchange resin	>78	92CL2357, 92MI2
(26), (27)		Anion-exchange resin	>81	92UP2

^a See Table I.

^b II.A.1, Eq. (1).

^c II.A.1, Eq. (4).

^d II.A.5, Eq. (23).

^e IV.D, Eq. (40).

^f 2-Benzimidazolate.

^g 5-Tetrazolate.

^h 4-Nitro-2-benzimidazolate.

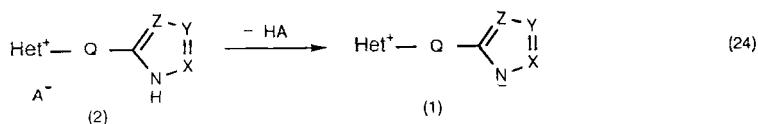
ⁱ III.A.3.

^j Eq. (26).

more specific Ortoleva–King reaction [73JHC899; 74HC(1)309] has yet been used, nor have the other methods for obtaining pyridinium quaternary compounds [74HC(1)309].

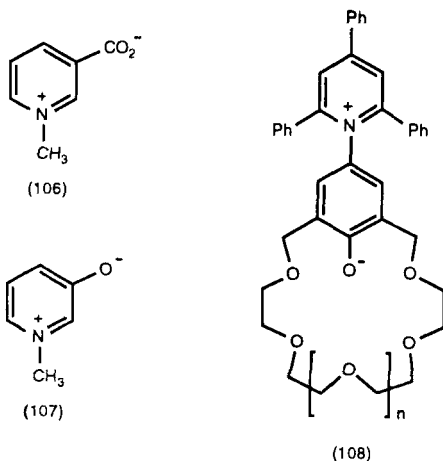
B. PYRIDIUM (IMIDAZOLIUM) AZOLATE BETAINES FROM AZOLYLPYRIDIUM (IMIDAZOLIUM) SALTS

The simplest synthesis of the title inner salts, including molecules with a betaine character of general structure **1**, is based on deprotonation of their immediate precursors **2** [(Eq.24)]. To remove the acidic NH proton of the azole nucleus and the inorganic counterion in compounds of type **2**, the necessary basic reaction conditions can be generated by either a strongly basic anion-exchange resin (OH^- form) or using other basic reagents (Table V).



1. Using an Anion-Exchange Resin

Applications of ion-exchange resins to a variety of chemical reactions are known (67M11; 74M11). They have proven to be extremely useful mainly due to their insolubility in water and organic solvents, which allows the resin to be removed by filtration without leaving undesirable ions



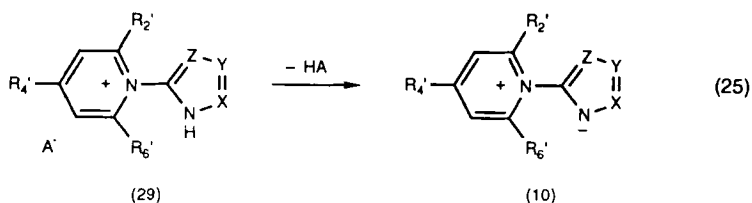
in solution (i.e., 89JOC4993; 90S735; 92JOC4834, 92S355). Basic anion-exchange resins have been used to obtain, for instance, betaines **106** (61JOC1318), **107** [71JCS(C)874], and **108** [91AG(E)558] by deprotonation of their corresponding quaternary pyridinium salts.

Almost all betaines and compounds with a betaine character of general structure **1** have been conveniently prepared applying this procedure (Table V; IV,C). Strongly basic anion-exchange resins were found to be satisfactory, and the chloride form of the resin was converted to the hydroxide form before use (76OS3; 87JOC5009; 92JOC4834).

2. Other Basic Media

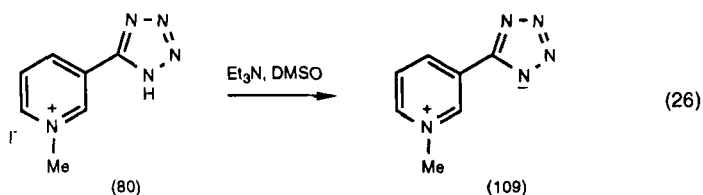
The scope of deprotonation of quaternary heteroaromatic salts of type **2** with common basic media is not too great and the isolation pure compounds of general type **1** may be difficult.

Some inorganic and organic bases have been used to obtain several examples of deprotonated compounds **10–13**, as shown in Table V. The first example was the transformation of *N*-benzimidazolylpyridinium perchlorate **55** into the *N*-ylide **56** using aqueous ammonia (66T3369) [Eq.(1)] and other examples in this series have already been discussed [Eq.(4) and (5), II,A,1; Eq.(25), II,A,5]. A comparative study of the transformation of *N*-azolylpyridinium salts **29** into the mesomeric betaines **10** has been performed using different procedures (87JOC5009) [Eq.(25), Table V, IV,D,Eq. (40)] and the method of choice makes use of a strongly basic anion-exchange resin (OH⁻ forms), as mentioned above.

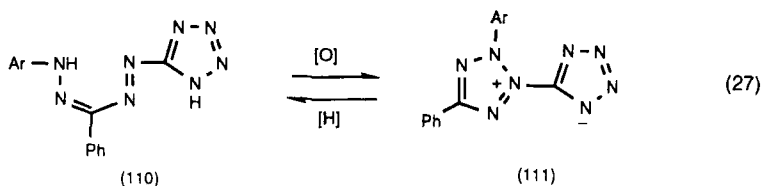


For these deprotonation procedures, the solubility of the ionic species present in the reaction mixture is of crucial importance. Although their solubility in water and in organic solvents might vary to some extent with their structure, the problem of isolation of pure target compounds of type **1** may sometimes be serious. In this connection, two examples of mesomeric betaines **10** reported by Dorofeenko and co-workers (78KG944) have been rechecked (87JOC5009, Table V).

Using triethylamine as a base, the pyridinium iodide **80** has been transformed to the new tetrazolate betaine **109** [82JCR(S)122] [Eq.(26), II,A,1,Eq.(12)].



Formazans **110** have been oxidized in aqueous alkaline solution with K_2MnO_4 or $\text{K}_3\text{Fe}(\text{CN})_6$ to the tetrazolium tetrazolate betaines **111** (73KGS1570; 74KGS268) [Eq.(27)].



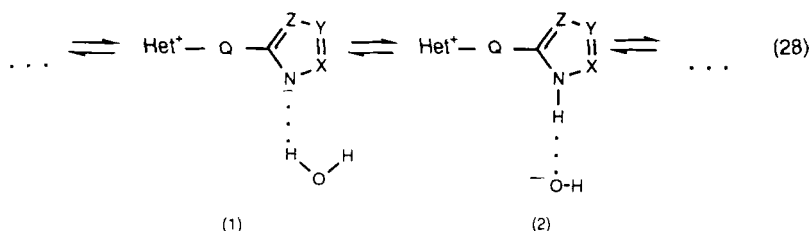
III. Structure and Physical Properties

Pyridinium(imidazolium) inner azolate salts and molecules with a betaine character of general type **1** are attractive substrates from the viewpoint of structural chemistry, as mentioned in the Introduction. This ensemble of compounds offers the possibility of two terminal heterocyclic rings, joined through several spacers, with extreme characteristics within heteroaromatic systems: a π -deficient nucleus (cation) and a π -excessive nucleus (anion). The high dipolar character is the distinctive feature offered by these compounds and has a powerful influence on their physical and chemical properties.

At present, the accessible physico-chemical properties have been studied mainly in liquid solution and the overall results provide evidence of their intrinsic high dipolar character. Moreover, compounds of type **1** may be ideal substrates for the study of their photophysical and other physical properties, especially for unconventional extended π -systems **15–20**, which are push–pull aza analogues of (*E*)-stilbene. Their capacity for specific physical behavior merits further exploration.

The dipolar structural pattern that characterizes these betaines implies strongly intermolecular forces (88MI1, 88MI2, 88MI3; 90JA5525; 92MI1). When two dipolar molecules are in optimal orientation to each other formation of nonpolar dimers in antiparallel arrangement may be favored (88MI1) and may cancel their dipolar moments, thereby lowering electro-

static energy. Thus, the effect of self-association for molecules of type **1** should be taken into account for reliable interpretation of solution data (III,B). Another interesting aspect arises in connection with the nature of the ionic species detected in solution, since the negative part of dipoles **1** are basic azolate moieties (87AHC187), especially for nonconjugated π -electron systems (III,E). The role of preferential interactions between water molecules and betaines **1** should also be taken into account. A plausible water-mediated proton path is shown in Eq.(28).



Both the effect of self-association and the presence of salt-type associates **2** [Eq.(28)] may modulate the physico-chemical parameters measured in solution. To reduce the perturbing dominance of these effects as far as possible, high dilution of the anhydrous sample **1** should be used and the water in the solvent should be reduced (III,B,C and E).

The physical intermolecular solute-solvent interaction forces (88MI1) as well as the solute-solute interactions should be taken into account for reliable interpretation of physico-chemical data measured in solution. Further structural studies may enhance our understanding of these highly dipolar organic molecules through their role in noncovalent interactions both in liquid solution and in solid state.

A. SPECTROSCOPIC PROPERTIES

1. Infrared Spectra

The reported IR spectra were recorded for solid samples of compound pairs **1** and **2**. The azolypyridinium(imidazolium) salts with several interannular linkages **2** have shown absorptions in the ranges $3500\text{--}3200\text{ cm}^{-1}$ (νNH) and $2800\text{--}2490\text{ cm}^{-1}$ (hydrochlorides) or $1100\text{--}1000\text{ cm}^{-1}$ (tetrafluoroborates). These bands were absent for the corresponding inner salts and compounds with a betaine character **1**. Practically all reported information concerning IR spectra and elemental analysis are included in the references quoted in Tables II to V (II,A and II,B).

2. Nuclear Magnetic Resonance Spectra

^1H and ^{13}C NMR studies on neutral azoles and pyridinium quaternary salts is by now a well-documented subject, and to a lesser extent, azolium quaternary salts. In contrast, only few studies have been devoted to azolate ions and practically all the reported data for the anion species have been generated *in situ* using the appropriate NMR solvent in basic medium, often because the azolate anions themselves are unknown.

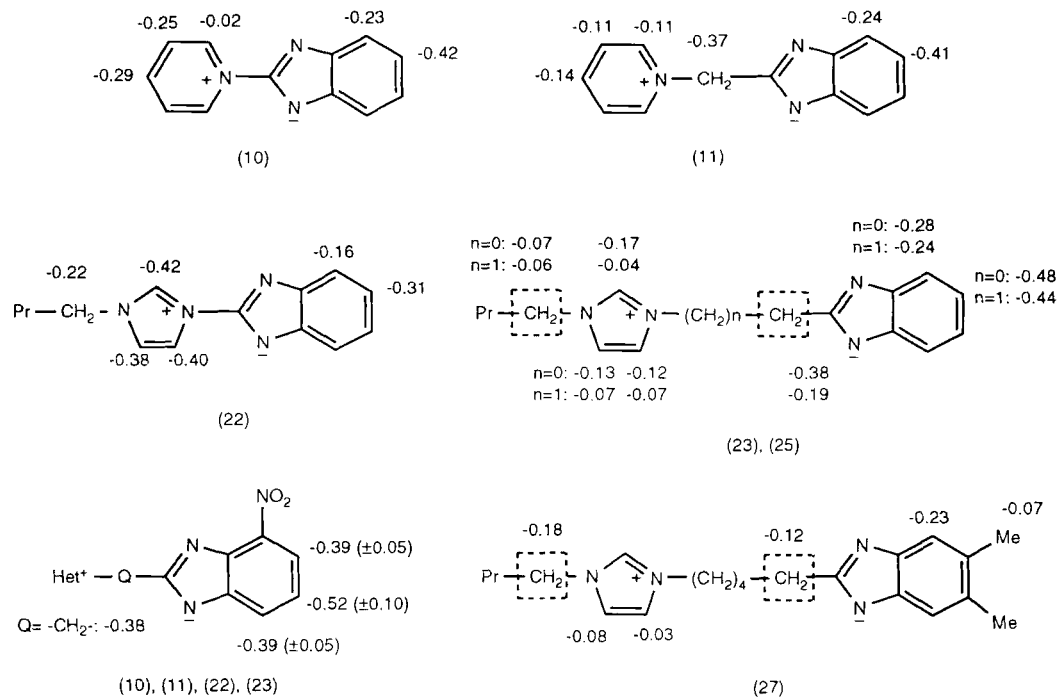
The NMR spectra of heterocyclic betaines and compounds with a betaine character **1** may lead to a deeper insight into their dipolar nature. Both ^1H and ^{13}C NMR results have proved to be crucial for structural proof and also for providing evidence of charge distribution within the molecule; the choice of the solvents was dictated by the solubility of the compounds **1**. ^{15}N NMR and high-resolution solid-state ^{13}C NMR spectroscopy have not been yet used to study the betaines referred to above.

For proton spectra, the CH protons of the azole ring are shifted to lower frequencies in the anion than in the neutral molecule [67JCS(B)516; 68JA4232; 71JA1880; 77MI1; 81OMR219]. The dipolar character of compounds **1** is reflected by ^1H NMR; the chemical shifts of the CH protons in the π -excessive nucleus were shifted upfield from the protons of their corresponding precursors **2**, and they are consistent with ^1H NMR chemical shifts for anionic species in the azole series. Differences in the chemical shift values ($\Delta\delta\text{H}$, Schemes 5 and 6) between selected examples of compounds **1** and their precursors **2** indicate the dipolar nature of **1**.

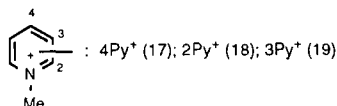
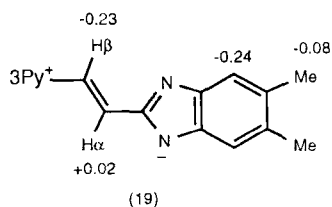
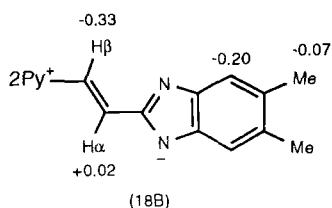
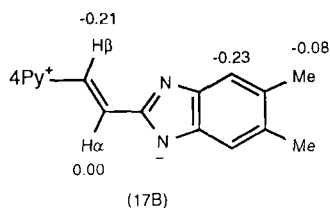
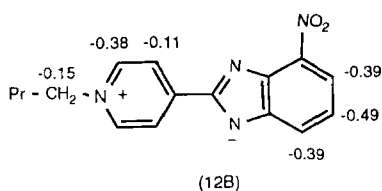
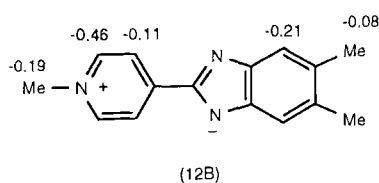
Aza analogues of sesquifulvalene **12** and their vinylogues **17** and **18** can be described to a first approximation by a covalent resonance form (**A**) and a dipolar one (**B**), whereas structures of type **19** may only exist as betaines. Comparison of the chemical proton shifts observed for compounds **12** and **17–19** with those of their corresponding precursors **31**, **36–38** ($\Delta\delta\text{H}$, Scheme 6) deserves a brief comment.

For aza analogues of sesquifulvalene **12** (**A** \leftrightarrow **B**), the CH proton signals in the six-membered ring move upfield with respect to their precursors **31** and the $\Delta\delta\text{H}$ values are similar to those observed for their corresponding analogues, the *N*-ylides **10** (Schemes 5 and 6, 91JOC4233). In both series, **10** and **12** (**A** \leftrightarrow **B**), δCH for the benzimidazole moiety is well correlated, providing evidence of the betaine character in solution for compounds **12** (III,B,C).

A similar situation holds for the extended π -systems of type **17–19**. Comparison of the chemical proton shifts observed in compounds of type **17–19** with those of their corresponding (benzimidazolylvinyl)pyridinium salts **36–38** ($\Delta\delta\text{H}$, Scheme 6) reveals a remarkably constant difference, irrespective of the substitution pattern between the π -excessive moiety



SCHEME 5. $\Delta\delta\text{H}$: Observed proton chemical shift difference (ppm; DMSO- d_6) between selected examples of betaines of type (10) (i.e., (55)), (11), (22), (23), (25) and (27), and their corresponding precursors the benzimidazolylpyridinium (imidazolium) salts of type (29) (i.e., (54), (30), (41), (42), (44), and (46) (87JOC5009; 91JOC4223; 92CL2357, 92JOC4829, 92MI3, 92UPI).



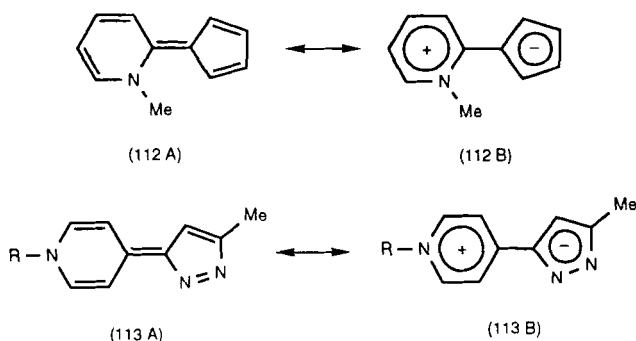
SCHEME 6. $\Delta\delta\text{H}$: Observed proton chemical shift difference [ppm; DMSO- d_6 for (12), (17), and (19); CD₃OD for (18)] between selected examples of compounds with a betaine character (12), (17), (18) and betaines (19), and their corresponding precursors benzimidazolypyridinium salts of type (31), (36)–(38) [89CC1086; 91CL2151, 91JOC4223; 93CP(614)].

and the vinylene interannular linkage. Several examples of compounds **17** and **18** in which the π -excessive moiety is an imidazole nucleus have shown similar chemical shift value differences ($\Delta\delta\text{H}$), providing evidence of the dipolar nature for compounds of type **17** and **18** in solution. With regard to the π -deficient moiety, the ^1H NMR signals are in good agreement with data for quaternary heteroaromatic compounds (87JOC5009; 91JOC4223).

Among the difference types of olefins known with barriers to rotation amenable to study by dynamic ^1H NMR technique, the reported rotational barriers of push–pull ethylenes containing potentially heteroaromatic systems are rather low, ca. 50 kJ·mol⁻¹ [85MI1; 88AHC(43)173]. Moreover, Elguero and co-workers have studied the rotational barriers around the C—C interannular bond of several 2-(4-pyridyl)benzazoles and their pyridinium salts (areno-analogues of amides), since they are too low to measure by ^1H NMR (60 MHz) at 173 K (77H911).

The only reported data concerning aza analogues of sesquifulvalene of type **4**, **5**, **12** and **13** (I, Scheme 2) refer to molecules of type **5** and **12** (67JA5384; 91JOC4223) (III.D.).

Compound **112** (**A**↔**B**) shows a barrier to rotation of $47.42 \text{ kJ}\cdot\text{mol}^{-1}$ at 223 K (67JA5384). Regarding experimentally rotational barriers of compounds with a betaine character **12**, the pyrazole derivatives **113** (**A**↔**B**) can serve as models. At 243 K the decoalescence was still distant for compound **113b** ($R \equiv \text{Bu}$) and its rotational barrier may thus be situated below $49.1 \text{ kJ}\cdot\text{mol}^{-1}$ (88TH1; 89CC1086; 91JOC4223) (III,D, Table IX).



^1H NMR spectra of several examples of the title compounds **1** were measured in $\text{DMSO}-d_6$ with ca. 10% TFAA and the chemical shifts were similar to those observed for their corresponding precursors **2**, which reversibly regenerated the dipolar compounds on treatment with 25% ammonium hydroxide. This assay is limited to dipolar compounds **1** that are stable in solution (88TH1; 91TH1; 92TH1).

Inspection of the ^{13}C NMR parameters for compound pairs of general type **1** and **2** shows that the δC values of the carbon atoms of the π -excessive nucleus are in good agreement with data reported for anionic species in the azole series (68JA4232; 71JA1880; 77MI1; 81OMR219; 87JOC5009). With regard to the π -deficient moiety, the δC signals correspond to quaternary heteroaromatic compounds (91JOC4223).

The deshielding effect at C-2 in the benzimidazole series **10–12**, **22–27** and imidazole series **17**, **18** is the most characteristic feature in ^{13}C NMR spectra of these dipolar compounds and reveals a quite constant $\Delta\delta\text{C}_2$, irrespective of the nature of the interannular spacer (Table VI and Scheme 7). One interesting aspect concerns the carbon chemical shifts for the (*E*)-vinylene interannular linkage for compounds with a betaine character **17**, **18** (Table VI). The change observed in the position of $\text{C}\beta$ resonances is in agreement with the β -substituent effects in the ^{13}C NMR chemical shifts of a series of β -heteroaryl styrenes [88JCS(P2)19; 90JCS(P2)645].

TABLE VI
MEAN VALUES OF OBSERVED CHEMICAL SHIFT DIFFERENCE ($\Delta\delta\text{C}$), BETWEEN
COMPOUND PAIRS **1** AND **2**

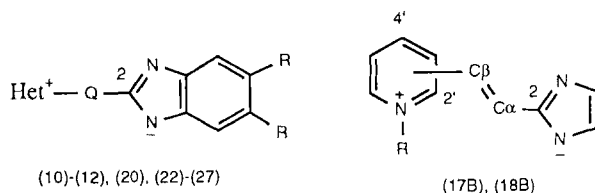
Compound ^a	Solvent	$\Delta\delta\text{C-2}$	$\Delta\delta\text{C-}\alpha$	$\Delta\delta\text{C-}\beta$	Reference(s)
(10), (11)	DMSO- <i>d</i> ₆	+9.0	—	—	87JOC4573, 87JOC5009, 88TH1; 91JOC4223
(12)	DMSO- <i>d</i> ₆	+7.5	—	—	88TH1; 91JOC4223
(22), (23)	DMSO- <i>d</i> ₆	+8.0	+4.0	—	91TH1; 92JOC4829
(24), (25)	DMSO- <i>d</i> ₆	+8.9	+3.4	+1.7	91TH1; 92CL2357
(26), (27)	DMSO- <i>d</i> ₆	+9.3	+2.3	+1.0	92UP2
(17), (18)	CD ₃ OD	+7.6	+8.0	-8.6	92JOC4834, 92TH1
(20)	CD ₃ OD	+6.6	+5.4	-4.0	92CL1779, 92TH1

^a See Scheme 7.

The positions of the resonance signals are often affected by nonspecific and specific solvent effects (88MI1). Among them, the intermolecular hydrogen-bonded solute-solvent complexes shown in Eq.(28) and the proton-transfer equilibrium can modulate on the observed chemical shift values for dipolar compounds **1** (88TH1; 91TH1; 92TH1). However, the overall results reflect the dipolar character in solution for the title compounds **1**. Further NMR studies may allow a deeper understanding of their intrinsic dipolar nature with concomitant presence of noncovalent interactions.

3. UV/Vis Spectra

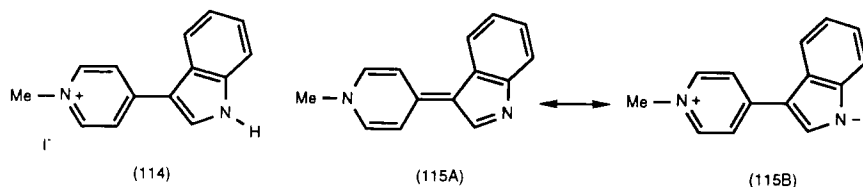
The long-wavelength UV/Vis absorption band of the 2-(1-pyridinio)-benzimidazolate **55** shifts from 445 nm in benzene to around 360 nm in water (66TL3369) or aqueous buffer at pH 9 (87JOC4573), and a hypsochromic shift in the spectra of two examples of *N*-ylides **104** [II,A,5, Eq.(23)], relative to betaine **55**, has been observed (87JOC4573). For *N*-pyridinium cyclopentadienide **9**, a solvent change from heptane to water causes a hypsochromic shift of ca. 90 nm (59JA856; 66TL3369; 88MI1). The negative solvatochromism of the *N*-ylides **9**, **55**, and **104** is much less pro-



SCHEME 7.

nounced than that for Reichardt's dye **49** and other related pyridinium *N*-phenolate betaines (88MI1; 91JOC568), including the novel chromoionophoric betaines **106** [II,B,1 (91AG(E)558; 92CSR147]. Moreover, the UV/Vis absorption spectrum of **49** has been determined in over 270 pure organic solvents and in several mixtures of organic solvents used to define an empirical parameter for solvent polarity, the E_T (30) values. Obviously, acidic solvents are excluded due to the fact that protonation of the phenolate anion of betaine **49** prevents the change in its dipole moment on electronic transition (88MI1). On the other hand, the electronic spectra of polycyclic aromatic cations have recently been reviewed (92AHC261).

The electronic absorption spectra for several mesomeric betaines **10**, i.e., **64** [II,A1,Eq.(4)] and **11**, i.e., **111** [II,B,2,Eq.(27)] has been reported (73KGS1570; 74KGS268; 75KGS987). Kost and co-workers (78KGS1481) have studied 4-(1*H*-indol-3yl)-1-methylpyridinium iodide **114** at different pH values in the range 7 to 13, and it was possible to determine the isosbestic point of the system formed by **114** and its corresponding anhydrobase **115** (**A**↔**B**), which is an example of aza analogues of sesquifulvalene with a betaine character **12**.



4. Mass Spectra

Betaines of general type **1** have not been systematically studied by mass spectrometry (MS). Only isolated data for several examples of compounds **11** and **12** have been reported (88TL491; 91JOC4223). It would be desirable to study this ensemble of compounds **1** using the appropriate MS techniques whatever they may be, together with their immediate precursors **2**. As for the azolylpyridinium(imidazolium) salts **2**, any of the MS methods that have proved to be adequate for quaternary pyridinium compounds may be used (83OMS52; 84JOC764; 87JOC4573; 90JA2471; 92TL7771).

B. DIPOLE MOMENTS

Dipolar moments appear to hold a certain fascination for theoretical chemists, who frequently check the validity of their calculations by com-

paring calculated dipolar moments with the corresponding experimental results (84MI3). Apart from the considerable interest from the physical chemical viewpoint, the applications of electric dipole moments to heterocyclic systems are of value from the biological and pharmacological viewpoint (63PMH189; 71PMH237).

In 1975 Mauret *et al.* (75BSF1675) carried out a detailed dipolarimetric study of the azole series, on the basis of the various, and sometimes conflicting, values of the dipolar moments reported in the literature. For pyrazole and imidazole, measurements were performed with the solvents dioxane and benzene at different concentrations and at 25°C, with the aim of determining the influence of concentration and solvent on the value of the dipolar moments, and, at the same time, the involvement of the different molecular associations owing to the formation of intermolecular hydrogen bonds. Thus, for imidazole (linear polymers), the dipolar moment increased with a rise in concentration, whereas for pyrazole (cyclic dimers), the dipolar moment decreased with higher concentrations, and consequently the dielectric permittivity fell.

In this connection, the dipole moment values for several examples of aza analogues of sesquifulvalene of type **4**, **5**, **9** have been reported [65JA2901; 70JCS(C)800] and for the *N*-ylide **9** was found to be 13.5 D (65JA2901) or 13.2 D (88MI4). For sesquifulvalene **3**, the μ_{exp} has been estimated to be 2.2 D (71MI1; 72C194). Among a selection of several representative solvatochromic compounds, the pyridinium *N*-phenolate betaine **49** has shown a high dipole moment in the ground state (μ_{g}) of 14.68 D, and 6 D in the excited state (88MI4).

The measurement of the dipolar moment of ionic compounds such as organic and inorganic salts is difficult. This is perhaps why there are few references in the literature. Thus, for example, Grunwald *et al.* focused on the study of the molecular structure of ion pairs from dielectric polar moments (74JA2387; 76JA1716) and the effects of solutes on hydrogen bonding in polar liquid solutions (76JPC2929).

In the area of heterocyclic mesomeric betaines of pyridinium azolate **10** and azolium azolate **11**, and in organic substrates with a marked dipolar character that are aza analogues of sesquifulvalene **3**, such as 1-alkyl-azoliden-1,4-dihydropyridines **12**, the experimental dipole moments of various examples of these series has provided us with a greater understanding of the electronic structure in the ground state of this group of compounds. In all cases they show high dipolar moments, in the range 9 to 13.5 D (Scheme 8 and Table VII) (87JOC5009; 91JOC4223). For the various cases studied, μ_{exp} values have been compared with μ_{calcd} (MNDO), as discussed later (IIID). In all cases, the measurement of the dipolar moment were extrapolated to infinite dilution ($\omega \rightarrow 0$) at 25°C, and the solvent used

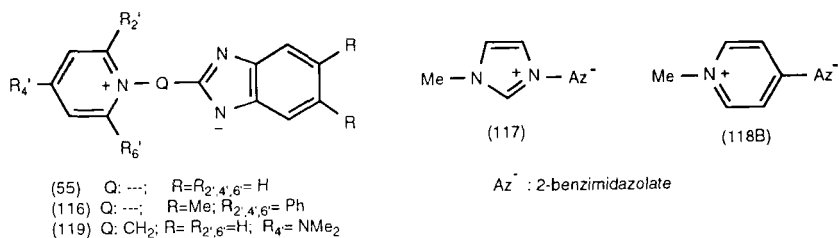
was anhydrous dioxane. The above system of measurement was used to dissociate, as far as possible, the nonpolar dimers (self-association) that bring about a reduction in the value of the dipolar moment and lower the electrostatic energy. Thus, when the concentration is increased ($\omega \geq 0.0002$), the dipolar moment tends to zero. It is also crucial that the solution be anhydrous (solute and solvent) to avoid hydration, which would lead to an erroneously high dipolar moment (91JOC4223). In summary, extreme, anhydrous dilution has always been used, which involves additional experimental difficulty in the measurement of dipolar moments in this group of structures **10–12** and, for that matter, any heterocyclic betaine or compound with a dipolar character **1**, due to the ease with which they are hydrated and form nonpolar associations in solution (even though dioxane is used at high dilution).

We can briefly summarize the results for **10–12**. For the first series studied, the betaines of pyridinium azolate **10**, the structures whose rings are coplanar, for example 2-(1-pyridinium) benzimidazolate **55**, are found to be strongly associated when the weight fraction (ω) is greater than 0.0002 and their dipolar moment tends to zero as concentration is increased. This clearly indicates an antiparallel arrangement forming nonpolar dimers. This orientation of **55** was confirmed by X-ray diffraction analysis, when this type of noncovalent intermolecular interaction was observed in the cell unit (III,C). In contrast, the betaines whose rings are arranged orthogonally do not associate at these concentrations, for example (2,4,6-triphenyl-1-pyridinium)benzimidazolate **116** (87JOC5009).

Measurement of the dipolar moments of the mesomeric betaines of azolium azolate **11** was extremely difficult. Of the various assays performed (extreme dilution, dioxane, 25°C), the best measurements were chosen. However, these quasi coplanar structures are highly associated when $\omega \geq 0.0003$, and the effect of self-association could not be eliminated completely. For example, for 2-(3-methyl-1-imidazolium)benzimidazolate **117** the μ_{exp} was 11.35 D and the antiparallel orientation of **117** was confirmed by X-ray diffraction analysis (III,C).

In similar experimental conditions, some examples of 1-alkyl-4-azoliden-1,4-dihydropyridines **12** were measured, the values of which ranged between 9 and 9.7 D. This implies a considerable separation of charges in the ground state, and also a dipolar nature, which was confirmed by X-ray diffraction analysis of 4-(benzimidazol-2-iden)-1-methyl-1,4-dihydropyridine **118** (III,C).

Different dipole moments measurements were determined for several examples of the ensemble of unconventional extended π -systems **17–20**, and the perturbing dominance of self-association has been a serious drawback (92PC1, 92TH1). It was, however, possible to record the dipole



SCHEME 8.

moment of three compounds from series **17–19**, which were found to be in the range 11.6 to 13.0 D (Table VII). For betaines **20**, the best recorded value were ca. 10.4 D (92CL1779, 92PC1, 92TH1). Unfortunately, the low solubility of 2-[4-(2,4,6-triphenyl-1-pyridinio)phenyl]-benzimidazoles **21** precluded the measurement of their dipole moments (87JOC5009).

The betaines of methylenepyridinium azolate **22** and methyleneimidazolium azolate **23** homologues of the *N*-ylides **10** and **11** have been studied in detail (92JOC4829). Dipolarimetric studies of four examples from this series were carried out in conditions similar to those used for the study of various examples of *N*-ylides (e.g., **55** and **117**). The experimental dipolar moments of these betaines of type **22**, **23** are found to range between 12.34 and 15.34 D (Scheme 8 and Table VII), which suggests a

TABLE VII
 RANGE OF DIPOLE MOMENTS FOR HETEROCYCLIC
 BETAINES (**10**), (**11**), (**19**), (**20**), (**22**), (**23**) AND COMPOUNDS
 WITH A BETAINES CHARACTER (**12**), (**17**), (**18**) IN DIOXANE
 AT 298 K

Structure	μ (D)	Reference(s)
(10)	10.33–13.52	86CC734; 87JOC5009; 88TH1
(55) ^a	10.33	86CC734; 87JOC5009
(116) ^a	≥ 13.0	86CC734; 87JOC5009
(11)	9.18–11.33	88TH1; 91JOC4223
(117) ^a	11.35	91JOC4223
(12)	9.0–9.7	88TH1; 91JOC4223
(118) ^a	9.03	91JOC4223
(17), (18)	11.66–11.94	91CL2151; 92JOC4834, 92TH1
(19)	13.0	91CL2151; 92TH1
(20)	≥ 10.4	92CL1779, 92PC1, 92TH1
(22), (23)	12.34–15.34	91CL845, 91TH1; 92JOC4829
(119) ^a	12.34	91CL845

^a See Scheme 8.

highly dipolar structure and a high separation of charge. However, the autoassociation effect was not completely eliminated, although the measurements were performed at high dilution ($\omega \leq 0.00015$). This again confirms the difficulty associated with the measurement of the dipolar moment of heterocyclic betaines that are susceptible to forming nonpolar dimers, even when conditions of extreme dilution in anhydrous solvents are used.

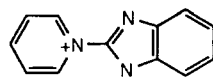
One of the more interesting structural features of small dipolar molecules of general type **1** is their experimental dipole moments, which merit further studies both in the ground (μ_g) and excited state (μ_e).

C. SINGLE-CRYSTAL X-RAY DIFFRACTION ANALYSIS

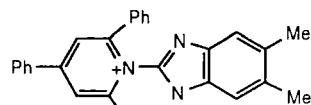
Among the variety of compounds emerging from prototype structures **10–28** mentioned in the Introduction (Table I), X-ray structural determinations have been performed on six representative examples: the mesomeric betaines **55**, **116**, **117**, and **120**; the higher homologue **119**; and the novel aza analogue of sesquifulvalene with a betaine character **118** (Scheme 9 and Table VIII). As mentioned earlier, the experimental dipole moments for molecules **55**, **116–119** were found to be in the range 9 to 13 D (III,B, Scheme 8 and Table VII). Comparison of the experimental molecular geometries and dipole moment values with those obtained from semiempirical molecular orbital calculations is discussed below (III,D).

Regarding mesomeric betaines, the interannular C—N' bond length is in the range 1.43 to 1.49 Å and the torsion angle between the weighted least-squares planes of the rings shows that molecules **55** and **117** are quasi-coplanar, whereas compound **116** adopts a nearly perpendicular arrangement (Table VIII, III,D). The 2,3,4-trisubstituted pyridinium benzimidazolate **120** is twisted ca. 63°. The 2-(1-pyridiniomethyl)benzimidazolate inner salt **119** has a central C—C—N' interannular bond angle of 111°. This value resembles that found for diphenylmethane (112.5°), the aromatic parent compound (81JOC4975).

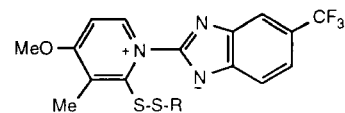
The molecular structure of 1-methyl-4-benzimidazolylidene-1,4-dihydropyridine **118** (**A**↔**B**) provides a definite structural assignment of several examples of aza analogues of sesquifulvalene with a betaine character **12** (**A**↔**B**), which lends credence to the spectroscopic results (III,A) and experimental dipole moments (III,B, Table VII). For compound **118** (**A**↔**B**), the interannular C—C' bond length is 1.448 Å, consistent with a C (sp^2)—C (sp^2) single bond and the molecule is effectively planar. Neither the benzimidazolate ring nor the pyridinium ring is symmetrical and the molecular bond lengths and angles correspond to the mean values,



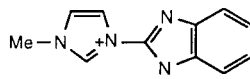
55
($\mu_{\text{exp}} = 10.33 \text{ D}$)



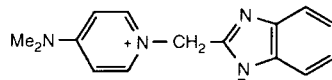
116
($\mu_{\text{exp}} \geq 13.0 \text{ D}$)



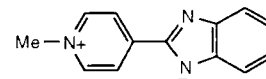
120 (R= $-\text{CH}_2\text{CH}_2\text{OH}$)



117
($\mu_{\text{exp}} = 11.35 \text{ D}$)



119
($\mu_{\text{exp.}} = 12.34 \text{ D}$)



118 B
($\mu_{\text{exp}} = 9.03 \text{ D}$)

SCHEME 9.

TABLE VIII
SELECTED CRYSTALLOGRAPHIC DATA OF COMPOUNDS **55**, **116**–**120**

Compound ^d :	55 ^b	116 ^b	117 ^c		118 ^d	119 ^e	120 ^f
			(A)	(B)			
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>a</i>		<i>I</i> 4 ₁ / <i>amd</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 1
C—N' (Å)	1.450	1.49	1.431	1.432		<i>g</i>	1.442
C—C' (Å)					1.448		
τ (°)	1.9	84.4	10.6	3.8	≤2.5°		≈63°
C—C—N' (°)						110	
D....A ^h (Å)		<i>i</i>	2.85, 2.88		2.97, 3.10	2.83, 2.90	
Intermolecular contacts	3.29–3.62 ^j		3.43 ⁱ , 3.46 ^j		3.60 ^j	3.33–3.47	

^a See Scheme 9. Designation: **116** = **116**·2H₂O, **117** = **117**·2H₂O, **118** = **118**·2H₂O, **119** = **119**·2H₂O.

^b 87JOC5009.

^c 91JOC4223.

^d 89CC1086.

^e 92JOC4829.

^f 87JOC4573, 87PC1.

^g C—N' (CH₂—N): 1.489 Å and C—C (C—CH₂): 1.498 Å.

^h H-bonds involving water molecules.

ⁱ See text.

^j Shortest contacts between the molecules in a type of antiparallel arrangement.

which are similar to the mean values for 2-(1-pyridinio)benzimidazolate **55**.

The crystal structure of compounds **55**, **116**–**119** supplies essential information on the spatial conditions of noncovalent interactive forces present in the solid-state buildup of these dipolar molecules. Mesomeric betaines **55** and **120** are unhydrated, whereas compounds **116**–**119** form a dihydrate and inspection of their corresponding unit cell reveals several aspects that deserve a brief comment.

The crystal packing of **55** has been shown to be in a type of antiparallel and displaced configuration and relevant intermolecular distances are ca. 3.45 Å, as listed in Table VIII. This fact corroborates the formation of nonpolar dimers in solution to explain the decrease of the experimental dipole moment when the concentration increases (III,B). The poor crystal quality of the inner salt (**116**·2H₂O) has limited the resolution of the data (*R* = 0.11, *R_w* = 0.12) and the two water molecules were disordered. It is, however, interesting to note that distances of **116**·2H₂O reveal a quasi symmetrical structure (87JOC5009) (III,B).

The crystal structure of 2-(3-methyl-1-imidazolium)benzimidazolate inner salt **117**·2H₂O is built by alternating layers of two symmetry-independent molecules (A) and (B), being parallel to the *c*-axis. The water molecules are predominantly placed between the layers and the H-bond interactions occur with the π -excessive moiety. On the other hand, the completely ordered molecules of type (A) are stacked pairwise in an antiparallel arrangement perpendicular to the *b*-axis (Table VIII).

The molecules of compound **118B**·2H₂O in the unit cell are parallel to the long faces of the unit cell, forming layers perpendicular to the *c*-axis. Each layer is built by alternating rows of **118B** molecules and H₂O molecules. The molecules of **118B** are antiparallel stacked; i.e., the nitrogen atom of the hexagonal ring of one molecule is located between the centers of the pentagonal rings of the two neighboring molecules in the row (Table VIII). In summary, all the experimental results of several examples compounds (**12** (A \leftrightarrow B)) are consistent with the betaine character of these compounds in the ground state, aromatization being the driving force (89CC1086; 91JOC4223).

X-ray analysis confirmed that the inner salt **119** forms a dihydrate and the water molecules are placed in rows along the *c*-axis. The H-bonds involving water molecules and the shortest contacts between molecules of **119** are collected in Table VIII.

Summing up, the crystallographic studies of the compounds referred above have been crucial for structural proof and also for providing evidence of the dipolar structure in the solid state within compounds of general type **10–12** and **22**. The large dipole moments in the ground state induce the molecules to pack in an antiparallel fashion to cancel their dipole moments, lowering electrostatic energy. The fact that the presence of salt-type associates mentioned before [Eq.(28)] has not been observed is noteworthy, and similar H-bond dimensions have been found for the dihydrates **116**, **117**, **118**, and **119** (Table VIII).

Unfortunately, crystallographic studies of other series within compounds of general type **1** are not always possible, owing to the lack of suitable single crystals under standard crystallization techniques. This is the case of compounds of type **17–20** (91CL2151; 92CL1779, 92JOC4834) and the unstable ethylenepyridinium(imidazolium) benzimidazolate inner salts **26**, **27** (91JOC6516; 92CL2357) (IV,C).

D. THEORETICAL METHODS

The duo formed by computational techniques and chemistry has become one of the most promising tools in the interpretation and analysis of

experimental data of existing molecules, and also for supplying information in molecular design of new compounds and structures [86MI1; 90AG(E)992, 90JMC833, 90N(L)631]. Amato (92SCI306) described the status of computational chemistry as the ascent of odorless chemistry. Calculation methods encompass MO and molecular mechanics techniques; each method is useful for certain purposes, and their significance to organic chemistry has been summarized by Streitwieser (90JOC7A).

The semiempirical MNDO SCF-MO and AM1 SCF-MO models introduced by Dewar *et al.* (77JA4899; 85JA3902) have proved to be suitable tools for reproducing experimental data for several examples of heterocyclic betaines of general type **1**, such as dipole moments and molecular geometries. Relevant results are collected in Table IX (III,B and C).

MNDO SCF-MO Hamiltonians were applied for several mesomeric betaines **10** (i.e., **55**) with a fixed geometry for both rings, and the interannular C—N' bond was taken to be 1.48 Å (87JOC5009). Some years later, the same technique but employing a standard *s/p* valence basis and with full optimization of all geometric variables was used for sesquifulvalene **3**, its aza analogues **4** (R = Me) and **5** (R = Me), and for four examples of type **12** (I, Scheme 2). A limitation of the MNDO method was found for structures of type **12** (**A** ↔ **B**) and the dipole moment was moderately well predicted for compound **118**, being rather low, but it was accurate for compound **121** (91JOC4223) (Table IX). An extensive theoretical study by semiempirical methods (i.e., AM1) is desirable for this type of structure **12** (**A** ↔ **B**) and their vinylogues **17** (**A** ↔ **B**), **18** (**A** ↔ **B**). On the other hand, three examples of pyridinium *N*-phenolate betaine dyes, including compound **49**, have also been studied by the AM1 method (91JOC568). The predicted dipole moment value in the ground state for Reichardt's betaine **49** was overestimated (Table IX).

The geometries of eight selected betaines of methylenepyridinium(imidazolium) azolate **22**, **23** (i.e., **119**, **120**) were constructed in Chem X (91MI1) and fully optimized at the RHF, closed-shell ground-state level using both the MNDO and the AM1 SCF-MO models, with the aim of evaluating which of these methods was the most suitable for structures of this type and, by extrapolation, for heterocyclic betaines of general type **1**. Comparison of the calculated molecular geometries of compound **119** with those obtained from its single-crystal X-ray diffraction analysis shows that the AM1 methodology provides a good description of the structure, which is slightly better than that described by the MNDO method. With regard to the dipole moments, the AM1 method predicts values closer to those experimentally determined than does the MNDO method (Table IX). Therefore, the AM1 SCF-MO is better suited to predicting experimentally observed trends of betaines of type **22** and **23**

TABLE IX
SELECTED SEMIEMPIRICAL CALCULATIONS DATA OF HETEROCYCLIC BETAINES **10**, **11**, **22**, **23** AND COMPOUNDS WITH A BETAINIC CHARACTER **12**

Structure	Method	ΔH_f (kJ·mol ⁻¹)	τ_{\min} (deg) calcd (exp)	d'' (Å) calcd (exp)	μ (D)		Reference(s)
					Calcd	Exp	
(3)	MNDO	400.56	0	1.368	1.29	ca. 2.2	71MI1; 91JOC4223
(4) ^b	MNDO	360.57	1.5	1.375	5.22		91JOC4223
(112) ^c	MNDO	379.23	10.2	1.378	3.02	5.20	63JOC1731; 91JOC4223
(12)	MNDO	304.12–453.34	0.0–0.3	1.381–1.398	7.69–9.34	9.03–9.71	91JOC4223
(113a) ^b	MNDO	355.23	0.1	1.381	8.87		91JOC4223
(113b) ^d	MNDO	304.12	0.1	1.381	9.34	9.42	91JOC4223
(118)	MNDO	453.34	0.3 (≤ 2.5)	1.395 (1.448)	7.69	9.03	91JOC4223
(10) ^e	MNDO		0–37.5		8.19–13.84	10.33–13.52	86CC734; 87JOC5009
(10) ^f	MNDO		90		10.15–15.52		86CC734; 87JOC5009
(55)	MM2//AM1		0.13 (1.9)	1.407 (1.450)	9.97	10.33	92PC2; 93JST105
(55)	MNDO	550.28	0.12	1.393	9.55	10.33	92PC2; 93JST105
(55)	AM1	685.40	0.12	1.398	9.41	10.33	92PC2; 93JST105
(55)	MNDO		0		11.06	10.33	86CC734; 87JOC5009
(11)	MNDO		0–52.5	1.403–1.422	8.52–14.76		91JOC4223
(117)	MNDO		0 (g)	1.413 (1.431) ^g	12.30	11.35	91JOC4223
(49) ^h	AM1		89	1.43	17.01	14.70	88MI4; 91JOC568

Structure	Method	ΔH_f (kJ·mol ⁻¹)	$N_1-C_0-C_1$ (deg) [calcd (exp)]	C_0-N_1 (Å) [calcd (exp)]	C_0-C_1 (Å) [calcd (exp)]	μ (D)		Reference(s)
						Calcd	Exp	
(22)	MNDO	455.47–532.08	107.6–108.8	ca. 1.544	ca. 1.467	14.34–17.13		92JOC4829
(22)	AM1	605.22–637.35	109.8–111.6	ca. 1.495	ca. 1.468	13.43–17.85		92JOC4829
(119)	MNDO	532	108.3 (111)	1.534 (1.489)	1.478 (1.498)	17.13	12.34	92JOC4829
(119)	AM1	642.95	110.5	1.484	1.484	17.85	12.34	92JOC4829
(23)	MNDO	373.59–428.40	108.2–110.4			14.34–15.76		92JOC4829
(23)	AM1	590.11–616.47	110.5–111.6			15.39–15.93		92JOC4829
(121) ⁱ	MNDO	347.29	108.7	1.532	1.463	15.49	15.34	92JOC4829
(121) ⁱ	AM1	605.76	111.6	1.476	1.467	15.39	15.34	92JOC4829

^a Interannular bond distance.

^b R = Me.

^c (112) ≡ (5, R = Me).

^d R = Bu.

^e R-2',4',6' = H.

^f R-2',4',6' = Me.

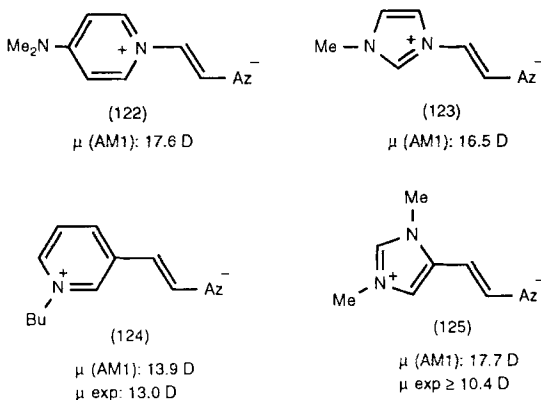
^g See Table VIII.

^h N-Pyridinium phenolate betaine (Reichardt's dye).

ⁱ 3-(3-Butyl-1-imidazoliumethyl)-1,2,4-triazolate.

than the MNDO SCF-MO (92JOC4829), and, from these results, of any heterocyclic betaine that emerged from the general type structure **1**. However, calculations on structures with a betaine character, such as **12**, **13** and their vinylogues **17**, **18**, need careful analysis for reliability.

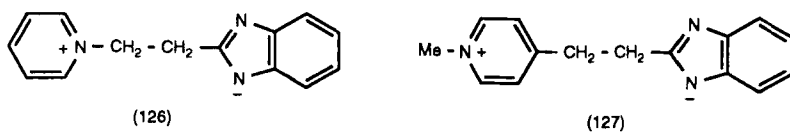
Running the calculations in the same way as for betaines **22**, **23**, four selected molecules, **122**–**125**, from the ensemble constituted by the inner salts **15**, **16** and **19**, **20** have been studied (92PC3). Both the AM1 and MNDO methods have predicted high dipole moments for the unknown betaines **122** and **123**, ca. 17 D. A similar situation holds for compounds **124** (13.9 D) and **125** (17.7 D), whereas the best measured dipole moment values were 13 D for **124** and >10.4 for **125** (III,B, Table VII).



(122), (123): Az⁻ = 2-benzimidazolate

(124), (125): Az⁻ = 5,6-dimethyl-2-benzimidazolate

Empirical force field calculations (MM2(8S)) using atomic point charges calculated by AM1 calculations (MM2 // AM1) correctly reproduce the AM1 surface for heterocyclic betaines **55**, **126**, and **127** (93JST105). The methodology allows extensive conformational analysis of medium to large-size molecules by semiempirical calculations (AM1). The interaction energies for the dimerization of these betaines have also been well reproduced.

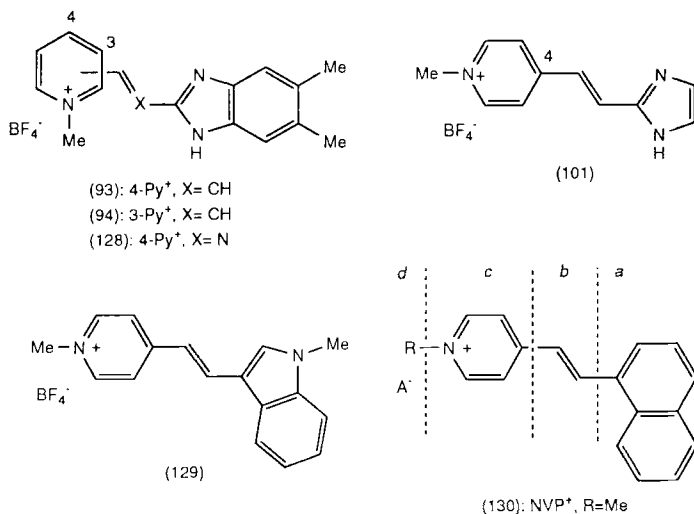


Dimerization of 2-(1-pyridinio)-benzimidazolate **55** has been observed in liquid solution (III,B) and in solid state, the shortest intermolecular contact being 3.29 Å (Table VIII,III,C). The antiparallel stacked structure

of **55** has been better predicted by the MM2 // AM1 calculations and the shortest atomic distance, at the energy minimum, was found to be of 3.37 Å, whereas using AM1 calculations it was 4.07 Å. On the other hand, a comparative study of MM2 // AM1, AM1, and MNDO calculations for all the energy minima of several model compounds has been performed including betaines **126**, **127** and their corresponding benzimidazolyethylpyridinium cations (compounds of type **43** and **47**) (93JST105).

A theoretical analysis of cations present in several examples of (*E*)-1-alkylazolyvinylpyridinium salts of types **36** and **38** has been recently reported (92MI4) (Scheme 10). Furthermore, a comparative study of semiempirical calculations using MNDO, AM1, and PM3 methods has been performed with cations of types **36**, **38** and the model **130** (92PC4).

Five selected cations, **93**, **94**, **101**, **128**, and **129**, together with the model compound **130** (NVP⁺, R=Me) were studied at the PM3 level (89MI1; 91MI1, 91MI2). At the final minima, all the compounds are planar, which, from the electron charge distribution, shows a degree of polarization similar to that of the NVP⁺ model compound **130** (Scheme 10). However, the fitting of all optimized structures indicated that only the indolylvinylpyridinium structure **129** showed the same orientation of the aromatic fragment *a* compared with the model **130**, leading to definition of a volume not accessible to ligands in the enzyme and consequently to a refined model of choline acetyltransferase (ChAT) recognition site (92MI4). The biological results are discussed in Section V.



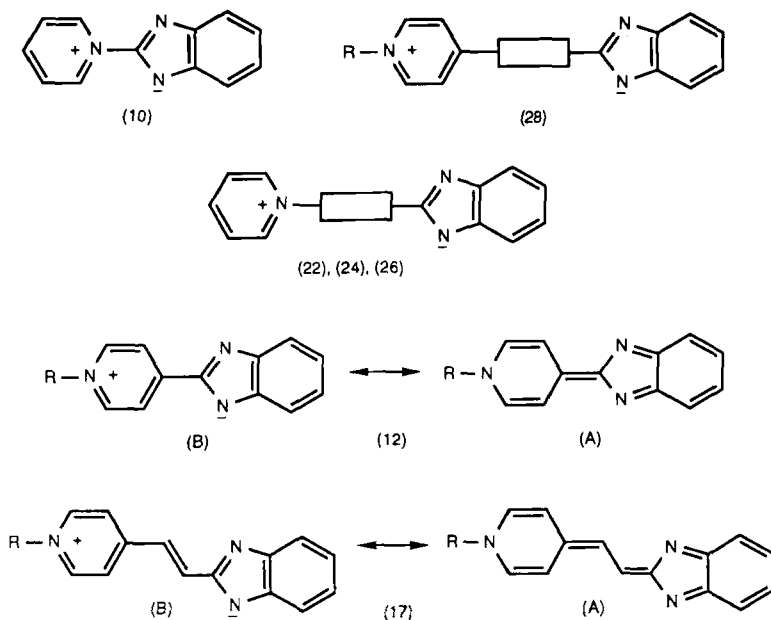
SCHEME 10.

E. OTHER PHYSICAL PROPERTIES

Different physical properties in both the ground and the excited states should provide deeper insight into the high dipolar nature of compounds of general type **1**. When the acid–base equilibria of these heterocyclic betaines are discussed, two situations must be considered: (i) there is resonance interaction between the pyridinium (azolium) cation and the azolate anion and (ii) the two moieties are independent.

In situation (ii), for instance betaines of type **10**, **22**, **24**, **26**, and **28**, the basicity of the benzimidazole anion is that of a classical benzimidazolate perturbed by the substituent at position 2. The pK_a values have been determined for betaines **10** and related compounds (87BSF604), allowing the determination of the σ meta value for the 2,4,6-triphenylpyridinium substituent ($\sigma_m = 0.67$, close to that of the nitro group, $\sigma_m = 0.74$). The main practical consequence is that betaines of these series are strongly basic compounds with a tendency to be solvated in order to gain stability. Situation (i) is quite different, e.g., **12**(**A** \leftrightarrow **B**), **17**(**A** \leftrightarrow **B**), since there is no formal negative charge on the benzimidazole ring; unfortunately, no pK_a values are available.

Unconventional extended π -systems of type **17–20**, and their immediate precursors **36–39** (Table I), should be of interest for their capacity for



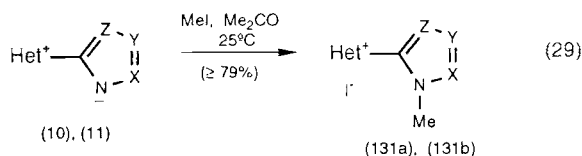
specific physical behavior in the field of advanced materials. Several molecules synthesized within these series (91CL2151; 92CL1779, 92TH1) have been selected for a preliminary study of their mesogenic behavior by means of optical microscopy (OM) and differential scanning calorimetry (DSC) as described by Serrano and co-workers (90M14), and none of them have shown a mesophase(s) (92PC5).

IV. Reactivity

Heterocyclic betaines and compounds with a betaine character of general type **1** are ideal substrates for the study of their chemical reactivity in both ground and excited states. The singular dipolar nature of **1** is a powerful driving force and this, together with the C—N' and C—C' bond types and the nature and length of the spacer, generates a wide range of possibilities for the study of their reactivity. Their chemical behavior toward dienophiles and their thermal and photochemical transformations (i.e., flash pyrolysis and photodimerizations) are aspects of interest at present.

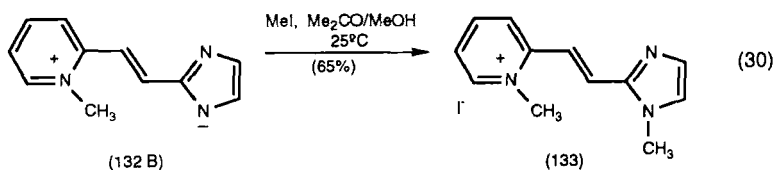
A. REACTIVITY TOWARD ELECTROPHILES AND DEQUATERNIZATION REACTIONS

It is well established that following *N*-alkylation of the azole nucleus by alkyl halides under neutral, but not usually mild, conditions the yields are restricted to around 50% (84M12), i.e., imidazoles [80AHC(27)241] and benzimidazoles (81HC86). Moreover, if the π -excessive nucleus is asymmetrically substituted, the corresponding regioisomers may be formed (II,A,1). Nevertheless, due to the highly dipolar structure of compounds of general type **1**, it could be expected that electrophilic attack at a nitrogen atom of the azolate ring would take place under neutral and mild conditions with yields of over 50%. Several mesomeric betaines **10** and **11** do indeed react with methyl iodide, giving their corresponding 1-methylazole quaternary salts **131a**, type **29** (*N*-Me), and **131b**, type **30** (*N*-Me), with high yields (90M13; 91JOC4233) [Eq. (29)]. For asymmetri-



cally substituted benzimidazole derivatives, both regioisomers have been found (91MI4; 92MI3).

A similar situation holds for several dipolar compounds **1** within other known series (Table I), if they are stable in solution. Among them, *N*-methylation of compound **132** (**A**↔**B**) has been reported (92JOC4834) [Eq. (30)]. Formation of the 1-methylimidazole quaternary salt **133** reflects the dipolar nature of compounds of type **18** (**A**↔**B**) together with **17** (**A**↔**B**), and this result is in agreement with the available physicochemical data measured in solution (III,A,2, Scheme 6 and Table VI; III,B, Table VII, being μ_{exp} of **132** = 11.66 D).

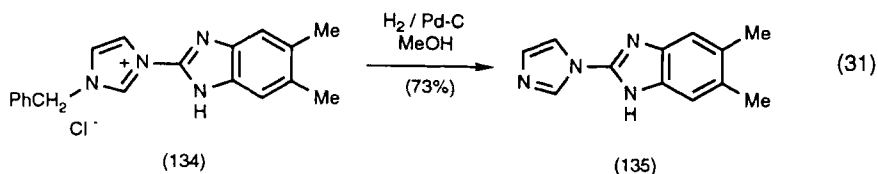


Quaternary salts of nitrogen heteroaromatic compounds are usually stable and their dequaternization reactions are of interest, being the reverse of the Menshutkin reaction (II,A,1). In this context, pyridinium salts and, to a lesser extent, condensed systems derived from six-membered nitrogen heterocycles are by far the most commonly investigated. This is presumably due to the fact that such studies were directed toward seeking insight into fundamental topics of heteroaromatic chemistry [79AJC1735; 81AJC163; 88AHC(43)173; 90CSR83].

Dequaternization of azolium quaternary salts initially involved pyrazolium compounds, which could be pyrolyzed in vacuum at ca. 200°C (66AHC417). The use of thiophenolate anion under phase transfer catalysis proved to be an excellent method of obtaining pyrazoles and indazoles in high yield from their corresponding quaternary salts [78CR(C)439]. The thermal decomposition of imidazolium quaternary salts has been studied by Grimmett *et al.* (77AJC2005).

As mentioned above, in the preparation of *N*-benzimidazolylpyrazolium chloride **65**, the formation of the dealkylated by-product **66** was detected at 135°C [II,A,1, Eq.(7)]. The more stable *N*-benzimidazolylimidazolium salts of type **30a** [Eq. (5)] were used as evidence, and thermolysis of three *N*-benzimidazolylimidazolium salts **30a** together with the *N*-benzimidazolylpyrazolium salt **65** was performed under standard conditions. On the other hand, debenzilation of the *N*-benzimidazolylimidazolium salt **134** by hydrogenolysis has been reported (91JOC4233) [Eq. (31)].

When planning the preparation of any member of the ensemble constituted by azolylpyridinium (imidazolium) salts **2** listed in Table I using any



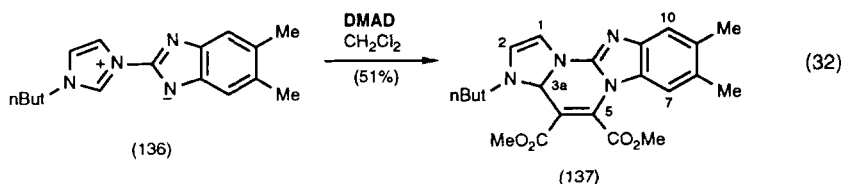
of the alternative routes discussed previously (II), attention should be paid to the reaction temperature to avoid dealkylation.

B. CYCLOADDITION REACTIONS

Cycloaddition reactions of mesomeric heterocyclic betaines, including meso-ionic heterocycles and heteropentalenes, have been the subject of extensive investigations [77T3203; 78AHC183; 80AHC(26)1; 82T2965], but none have dealt with the conjugated heterocyclic *N*-ylide **9** and related compounds (85T2239).

Heterocyclic mesomeric betaines **10** and **11**, aza analogues of the *N*-ylide **9** (I, Scheme 2), are suitable for studying their behavior as dipoles, where the dipolar moiety contains more than four π electrons. Moreover, their reactions with dipolarophiles should be a potentially attractive route for the synthesis of a variety of heterocyclic structures, and can also give entry into novel polycyclic ring systems.

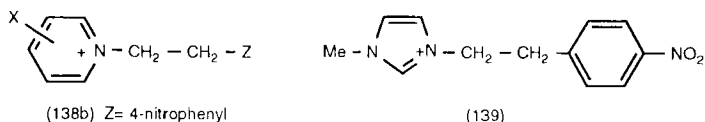
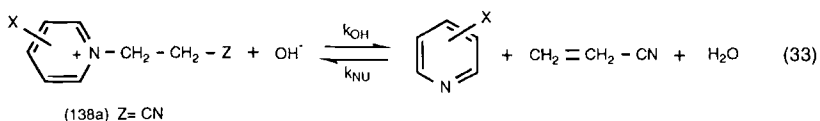
A preliminary investigation of the behavior of azolate azolium inner salts **11** toward dipolarophiles has been reported (91JOC4233). When equimolecular amounts of **136** and dimethyl acetylenedicarboxylate (DMAD) were mixed in dichloromethane at 25°C for 3 h, the major product was a 1 : 1 adduct, the new tetracyclic structure **137** [Eq. (32)].



C. β -ELIMINATION REACTIONS

Quaternary aza aromatic compounds are suitable substrates for investigating fundamental topics in organic chemistry. The behavior and use of pyridines as neutral leaving groups in nucleophilic substitution at a satu-

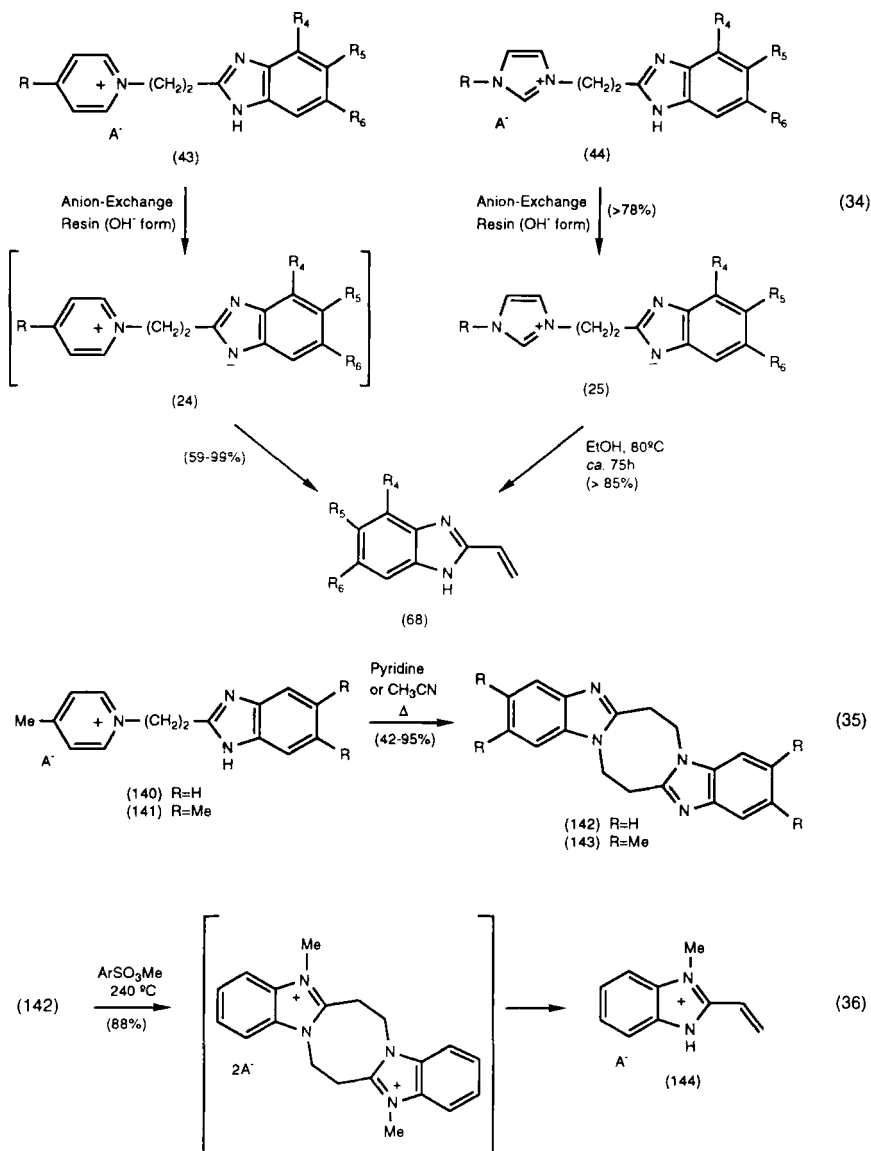
rated carbon atom have been developed by Katritzky and his group (90CRS83; 91JOC5039). Besides the synthetic value, this sheds light on the mechanism of aliphatic nucleophilic substitution reactions both in solution and in the gas phase. As for 1,2-elimination reactions, Bunting *et al.* have reported a detailed kinetic and mechanistic study for base-catalyzed E1cB reactions of *N*-(2-cyanoethyl)pyridinium cations **138a**, and the rates and equilibria for the Michael-type addition have also been studied (90JA8878) [Eq. (33)]. Furthermore, the results with several *N*-pyridinium cations **138b** and the imidazolium analogue **139**, with the same activating group, have shown that for leaving groups of similar basicity, pyridine is a better nucleofuge than 1-methylimidazole (91JA6950).



Several benzimidazolylethylpyridinium salts **43**, through the unstable betaines **24**, underwent a type of β -elimination and were transformed at room temperature into their corresponding 2-vinylbenzimidazoles **68** using a strongly basic anion-exchange resin, hydroxide form (II,B,1). This approach allows a practical synthesis of the almost unknown 2-vinylbenzimidazole monomers (91JOC6516) [Eq. (34)]. Due to the instability of simple inner salts of type **24**, it was only possible to detect these species from 4-nitrobenzimidazole derivatives by ^1H NMR (D_2O - NH_4OH) (91TH1) (see below).

The chemical behavior of benzimidazolylethylimidazolium salts **44** under basic and neutral media has been reported (92CL2357, 92MI2). As outlined in Eq. (34), deprotonation of compounds **44** afforded the fairly unstable ethyleneimidazolium benzimidazolate betaines **25** (but less so than **24**), which underwent a type of β -elimination at 80°C and 2-vinylbenzimidazoles **68** were formed.

For quaternary salts **43**, Katritzky and co-workers reported that compounds **140** and **141** were converted into cyclic dimers **142** and **143**, their structure being verified by X-ray diffraction of **142** [76JCS(P1)312] [Eq. (35)]. Methylation of dimer **142** led to 1-methyl-2-vinylbenzimidazolium salt **144** through an unstable intermediate, as shown in Eq. (36). It was



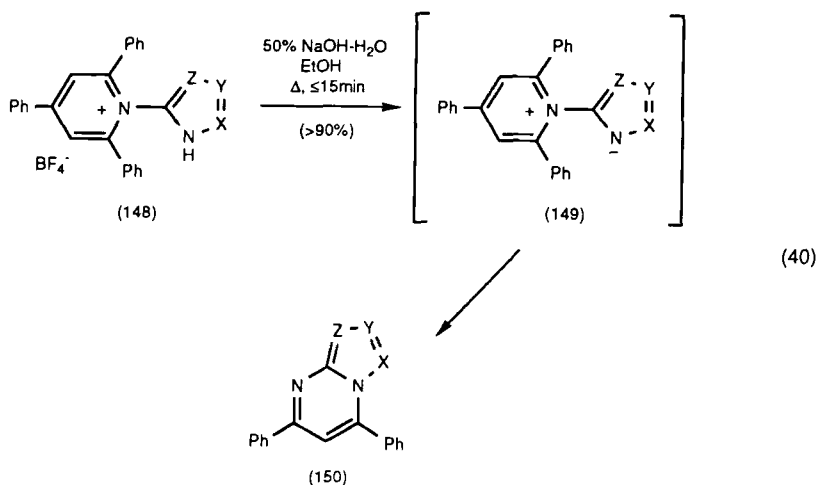
pointed out that the 1,5-diazocine system had to be formed directly from the starting salts **140**, **141** shown in Eq. (35).

As stated above in Eq. (34), the ability of the compound pairs **25** (i.e., **145**) and **44** (i.e., **146**) to undergo a type of β -elimination would be favored by the betaine structure **25**. The negative part of dipoles **25** are fairly

Both the inner salts of type **24**, **25** and their immediate precursors **43** and **44** may serve as suitable organic substrates for seeking insight into basic organic reactions and their mechanisms.

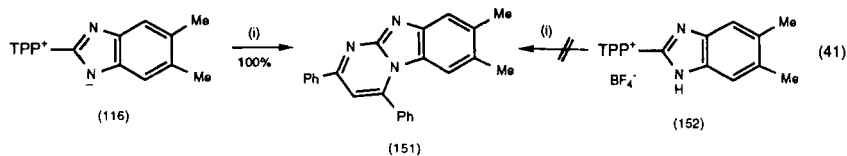
D. OTHER REACTIONS

One of the most familiar types of ring-opening among pyridine derivatives is associated with the reaction of pyridinium compounds with nucleophiles through an S_N (ANRORC) mechanism (81T3423; 85T237). As previously mentioned (II,B,2), several examples of the *N*-ylides **10** were prepared by deprotonation of their corresponding *N*-azolylpyridinium salts **29** using different basic media (87JOC5009) [Eq. (25), Table V]. However, the 2,4,6-triphenylpyridinium derivatives **148** (i.e., **85**, II,A,2) were converted into the corresponding azolopyrimidines **150**, via the known *N*-ylides **149**, when the basic medium was aqueous sodium hydroxide (88TH1; 92UP4) [Eq. (40)]. For asymmetrical azoles (i.e., 1,2,4-triazoles) only one regioisomer was found.

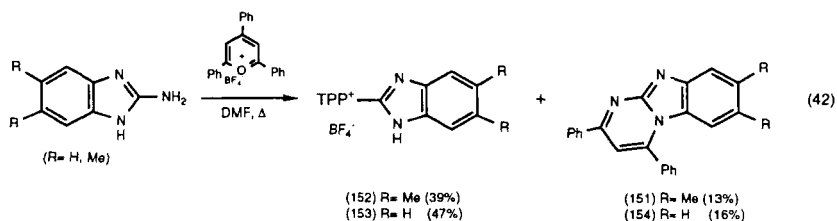


The mesomeric betaine **116** was quantitatively converted in refluxing EtOH-H₂O into the corresponding benzimidazo[1,2-*a*]pyrimidine **151**, whereas its precursor *N*-benzimidazolylpyridinium tetrafluoroborate **152** remained unaltered under the same reaction conditions [Eq. (41)]. On the other hand, benzimidazopyrimidine **151** was also formed as secondary product by using forced reaction conditions according to Eq. (42) for synthesis of compounds type **85**, i.e., **152** (87JOC5009) and **153** (75KGS1180; 82M11; 87JOC5009) (II,A,2, Table II).

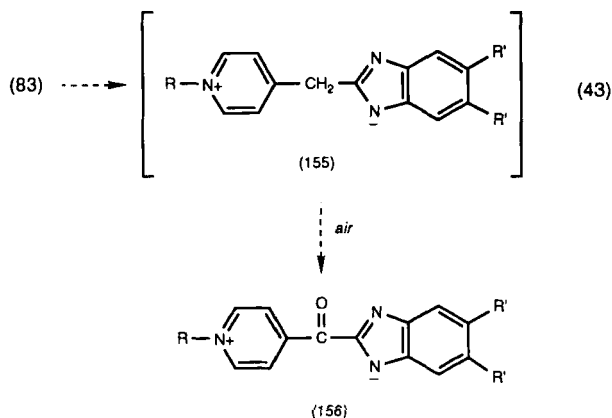
Owing to the finding that 4-(benzimidazolylmethyl)-1-alkylpyridinium salts **83** had been spontaneously transformed to the 4-(benzimidazolylloxomethyl)-1-alkylpyridinium analogues **84** (91TH1)[II,1,Eq. (13)], both preparation and isolation of the unknown betaines **155** with a C—CH₂—C'



TPP⁺: 2,4,6-Triphenyl-1-pyridinio; (i) EtOH-H₂O, Δ, ≤15^min



interannular spacer are likely to be difficult. According to Eq. (43), the high dipolar character of **155** will favor the oxidation to **156** through the captodative effect (88PAC1635). Compound pairs **155** and **83** have been omitted in Table I (I).



V. Biological Properties

The title dipolar molecules **1** and the protonated counterparts **2** encompass a vast array of compounds within the different patterns outlined in Table I (I) and the biological aspects of several members of these series have been investigated.

A variety of compound pairs **10**, **29** have been reported from a biological viewpoint (90MI2; 91MI3). In connection with the mechanism of

action and the underlying chemistry of the potent H^+/K^+ ATPase inhibitors PSP₅, **102**, previously mentioned [III,A,5, Eqs. (22)–(24)], several *N*-benzimidazolylpyridinium salts **103** (86JMC1327) together with the corresponding *N*-ylides **104** (86CC125; 87JOC4573) were formed through an acid-catalyzed pathway.

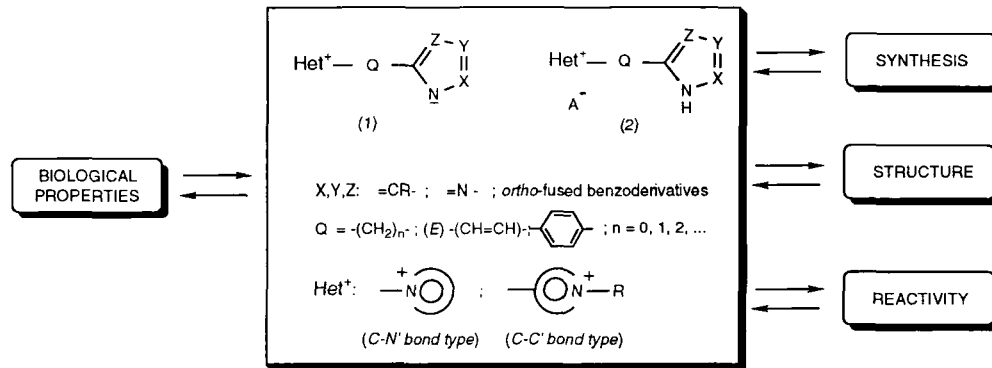
An antiparasitic screening of several model compound pairs **10**, **29** showed that some *N*-azolylpyridinium salts **29** demonstrated antileishmanial activity *in vivo* and also *in vitro* activity against *Trypanosoma cruzi* (88TH1; 90MI3). The selection of a representative subset of *N*-benzimidazolylpyridinium salts of type **29** was performed by means of a QSAR analysis [88TH1; 91MI4]. On the other hand, several compound pairs **11**, **30**, and **12**, **31** had exhibited antileishmanial activity, although to a lesser extent than the aforementioned compounds **10**, **29** (88TH1). Among compound pairs **10**–**12**, **22**, **24** and **29**–**31**, **41**, **43** containing a 4-nitrobenzimidazole moiety (91TH1), studies evaluating their activity against *Trichomonas vaginalis* demonstrated that some of the C–N'-type bond compounds had activity (i.e., **10**, **30**), although less than metronidazole, the reference drug (91TH1; 92MI3).

A series of *N*-pyridinium quaternary salts **29**, **41**, and **43** obtained from pyrylium salts (II,A,2) in which the π -excessive ring contains different annular heteroatoms (N, O, S) showed biological activity; they are described in the review of Balaban *et al.* (82MI2).

(*E*)-Alkylazolylvinylpyridinium salts **36**–**38** could serve as model compounds for testing their behavior as enzyme inhibitors, for instance **36** toward (H^+/K^+)-sensitive ATPase (91TH1; 93CPB614) or ChAT (92MI4; 92TH1). Regarding their behavior toward ChAT *in vitro* (III,D, Scheme 10), the (*E*)-indolylvinylpyridinium salt **129** is the only one showing some ChAT inhibition and a similar VDW surface to the reference NVP⁺ (**130**). The results suggest that the previously established (88JMC117) coplanarity and polarization criteria may not be enough to account for the ChAT inhibitory activity of aryl(heteroaryl)vinylpyridinium salts, and that steric requirements might have a very important role in their interaction with the enzyme (92MI4).

VI. Conclusions

Heterocyclic betaines of azinium (azolium) azolate with different interannular spacers **1** constitute a vast array of highly dipolar chemical entities with low molecular weight. In Scheme 2, it has been stressed that sesquifulvalene **3** can be broken down into various types of betaines and compounds with a betaine character. From the studies reviewed, it is apparent that Scheme 1 is transformed to Scheme 11. The present level of knowledge



SCHEME 11.

of the chemistry of betaines **1** is described in four interconnecting boxes. Future research will provide deeper insight into the chemical aspects of compounds **1** outlined in Scheme 11, and the more promising have been suggested in the corresponding sections (II–V).

An interdisciplinary approach should lead to their future prospects as building blocks of a variety of chemical structures. Thus, betaines **1** can be incorporated as a subunit(s) in host molecules and could confer unusual properties to the supramolecules, either cavitates or clathrates. Their capacity for specific physical behavior should also be considered together with their use as neutral ligands (azolate ligands without counterion) in forming metal complexes. Advances in the chemistry of betaines **1**, to be of any real significance, must result from coordinate efforts directed toward supramolecular chemistry, advanced organic materials, and heteroarene coordination chemistry.

Finally, there are aspects, some of basic interest, for which compounds **1** may be useful but for which different ideas will be required, beyond those suggested here, before a global perspective of this ensemble of dipolar substrates is achieved.

ACKNOWLEDGMENTS

The pathway leading to various heterocyclic betaines has been smoothed by a small team of talented collaborators, and leveled out by other colleagues thanks to their valuable assistance in theoretical, physical, and biological domains. I express my gratitude to all of them. My special thanks go to Dr. Jordi Frigola for continuous encouragement and stimulating discussions. I also thank Mr. Robin Rycroft for helpful discussions on semantics and style. Acknowledgment is further made to the Ministerio de Educación y Ciencia, DGICYT (PB 89-0214 and PB 92-0792), for financial support of this work.

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Cycloaddition Reactions of Nitrile Oxides with Alkenes

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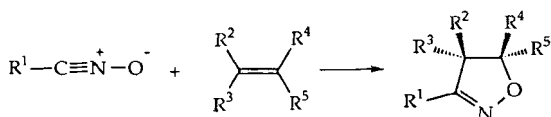
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I. Introduction

Reactions of nitrile oxides with alkenes to give Δ^2 -isoxazolines (hereinafter referred to as isoxazolines) (Scheme 1) have continued to attract attention since the pioneering work of Werner and Buss in 1894 (1894CB2193), Wieland in 1907 (07CB418, 07CB1667) and Quillico *et al.* in 1950 [50G479, 50N(L)226]. Huisgen categorized these processes as being members of the broad class of [3 + 2] cycloaddition reactions [61MI1; 63AG(E)565, 63AG(E)633]. Their mechanistic aspects have been the subject of considerable debate and, more recently, their synthetic potential has been the object of intensive study.

The extent and diversity of research in this area have led to earlier reviews (64MI1; 71MI1; 75ACR361; 77MI1; 83MI1; 84MI1; 88MI1; 91HC1). Caramella and Grünanger summarized work to 1980 as part of a review of the chemistry of nitrile oxides and imines (84MI1). Later, Grünanger and Vita-Finzi reviewed the synthesis of isoxazolines to 1984 (91HC1). Torssell surveyed the literature relating to the use of nitrile oxides, nitrones, and nitronates in organic synthesis to 1985, with an addendum incorporating work published before August 1987 (88MI1). The

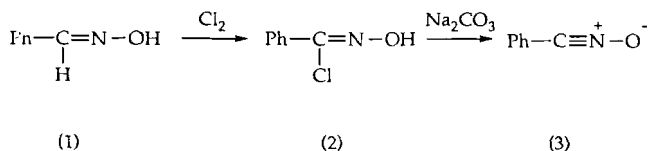


SCHEME 1

publication of more than two hundred papers since 1987 on reactions of nitrile oxides with alkenes is testament to the continued interest in the field and has prompted the current review, which covers literature published between 1985 and 1992. Some work from 1993 and unpublished material are also discussed. Earlier work has been included only where it is required to put more recent developments in context. Research trends are illustrated with representative rather than exhaustive examples. Particular attention is given to dramatic improvements in the degree of stereocontrol that has been attained in intermolecular reactions and to developments in the use of intramolecular nitrile oxide cycloaddition (INOC) reactions, where the predisposition of the reacting groups within a molecule greatly enhances the regio- and stereo-selectivity.

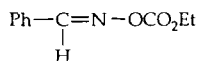
II. Nitrile Oxide Synthesis

The synthesis of benzonitrile oxide (3) by chlorination of benzaldoxime (1) to give benzhydroximinoyl chloride (2), followed by dehydrohalogenation with sodium carbonate (Scheme 2), as established by Werner and Buss (1894CB2193), formed the basis of what remains the most common approach for synthesis of nitrile oxides. Chlorination has been accomplished using chlorine, although ring chlorination occurs with aryl systems that are substituted with electron-donating groups (89CPB2519). Alternative chlorinating agents include nitrosyl chloride (27LA161), *N*-chlorosuccinimide (80JOC3916), hypochlorite (86SC763; 87TL3189), chloramine-T (*N*-chloro-*N*-sodio-4-methylbenzenesulfonamide) (89S57), 1-chlorobenzotriazole (90SC1373), iodobenzene dichloride (91SC1625), and hydrogen chloride in DMF/OXONE (92JOC1088). Tertiary amines, particularly triethylamine, are commonly used in place of carbonate [61AG656, 61TL583; 78JCS(P2)607]. Aluminium oxide (85T5569), Flori-



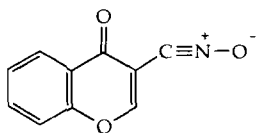
SCHEME 2

sil (85T5569), molecular sieves (90H1693), hexabutylditin (87SC1199), bis(tributyltin) oxide (91CC17), tetraphenyltin (91CC17), tributyltin hydride (91CC1671), and alkali metal fluorides (91H477) have also been used as dehydrohalogenating agents. Other variations include bromination instead of chlorination, using hypobromite (65JOC2809), sodium bromite with a catalytic amount of tributyltin chloride (89TL3987), or *N*-bromosuccinimide (68JOC476), and thermal dehydrohalogenation of the hydroximinoyl halide (63BSB719; 86MI1; 89JOC2209). Thermolysis has also been used to generate the nitrile oxide from the *O*-ethoxycarbonylaldoxime (4) (91BCJ318). Nitrile oxides have also been obtained through electrolysis of aldoximes in methanol containing sodium chloride (89JOC2249; 90MI1) and by oxidation of aldoximes with dimethyl dioxirane (92NKK420) or mercuric acetate (92OPP91).

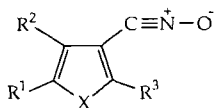


(4)

Examples of the variety of nitrile oxides that can be prepared from the corresponding aldoximes include the chromone derivative (5) (88H1127), the thiophene derivatives (6a) (88KGS1034; 89KGS1620; 91CCC1315), the furan derivatives (6b) (91CCC1315), the phosphorus-functionalized nitrile oxide (7) (86CL183; 87BCJ2463; 88BCJ2133; 89BCJ171), and the ribose derivative (8) (89TL3675). Dibromomaldoxime gave the nitrile oxide (9) in water, for direct reaction with water soluble olefins (92TL3113). Metal-chelated nitrile oxides (10) were obtained by treat-

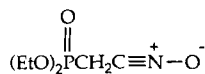


(5)

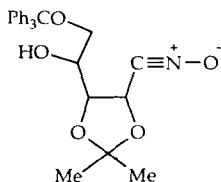


(6)

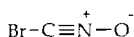
a) X = S
b) X = O



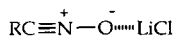
(7)



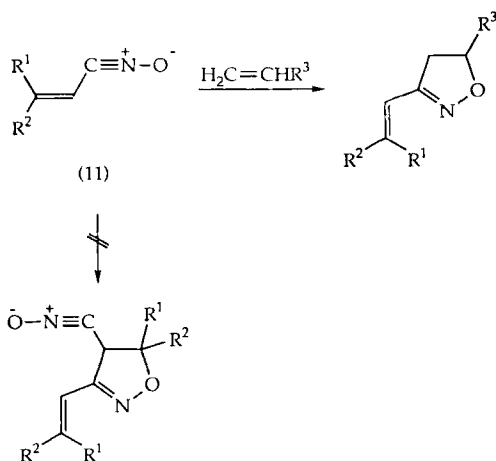
(8)



(9)



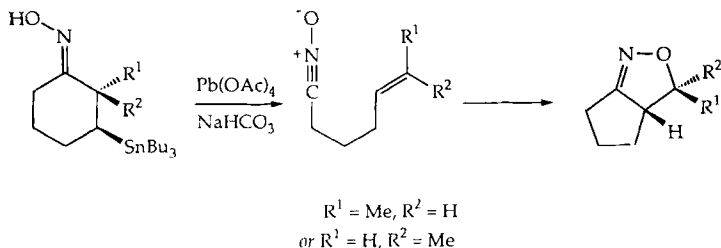
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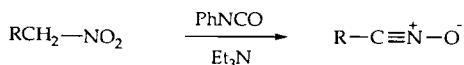
SCHEME 3

ment of benzhydroximinoyl chloride (**2**) with organometallics, and used to advantage in cycloaddition reactions, where complexation of the metal with the alkene improved the regio- and stereo-selectivity (91TL6367; 92TL1357). Of particular interest, the α,β -unsaturated nitrile oxides (**11**) were prepared by treating the corresponding aldoximes with *N*-chlorosuccinimide/triethylamine and used in cycloaddition reactions without competing self-condensation (Scheme 3) (90ACS806). A novel method of nitrile oxide synthesis was devised by Nishiyama *et al.* (85JA5310), whereby oxidative fragmentation of β -stannyl oximes gave nitrile oxides and alkenes simultaneously, with control of stereochemistry of the alkenes (Scheme 4).

An alternative common method of nitrile oxide synthesis, frequently referred to as the Mukaiyama method (60JA5339), involves dehydration of primary nitroalkanes using, for example, phenyl isocyanate in the presence of a catalytic amount of triethylamine (Scheme 5). Phosphorus oxychloride (73OS59; 90S817), chloroformate esters (86BCJ2827), aryl

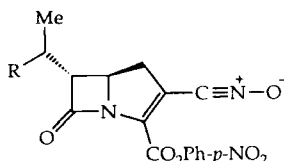


SCHEME 4

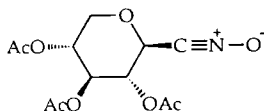


SCHEME 5

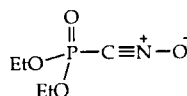
(86BCJ2827, 86M1091) and alkyl sulfonyl chlorides (89MI1), and acetic acid and anhydride (89MI1) have also been used as dehydrating agents, and thionyl chloride has been used with nitroacetamides (89TL3193). The versatility of the method using methyl chloroformate/triethylamine was illustrated through application with the labile carbapenem derivatives (**12**) (84CC1513). The nitrile oxide (**13**) was obtained from the corresponding nitromethylxylose by treatment with tolylene diisocyanate (88CC1339). The nitrile oxide (**14**) was produced from diethylnitromethylphosphonate using phosphorus oxychloride (90S817). The Mukaiyama method is preferable with substrates such as sulfides, which are susceptible to oxidation. Accordingly, nitrile oxides such as (**15**) (88BCJ3973) and (**16**) (90JOC5505, 90TL743) have been prepared from the corresponding nitroalkanes.



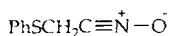
(12)



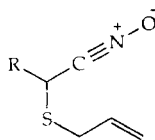
(13)



(14)

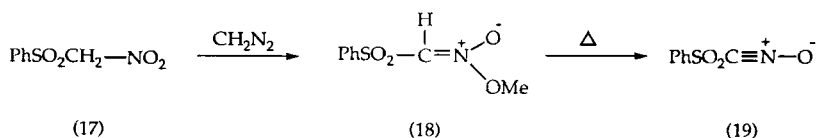


(15)



(16)

In related procedures acetyl chloride and acetic anhydride have been used to prepare nitrile oxides from lithium nitronates (86T3825), whereas the nitronic ester (**18**), prepared by *O*-alkylation of the nitroalkane (**17**), underwent thermal elimination of methanol to generate benzenesulfonylnitrile oxide (**19**) (Scheme 6) (84H2187). The latter procedure is potentially HAZARDOUS, as the nitronic ester (**18**) has been reported to be EXPLOSIVE (85JMC1109), and base-induced elimination of methanol from the

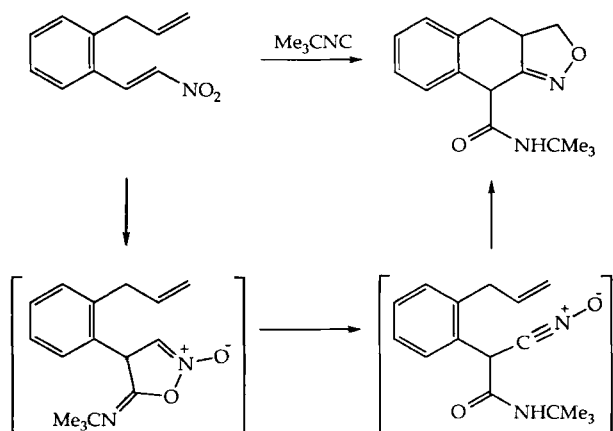


SCHEME 6

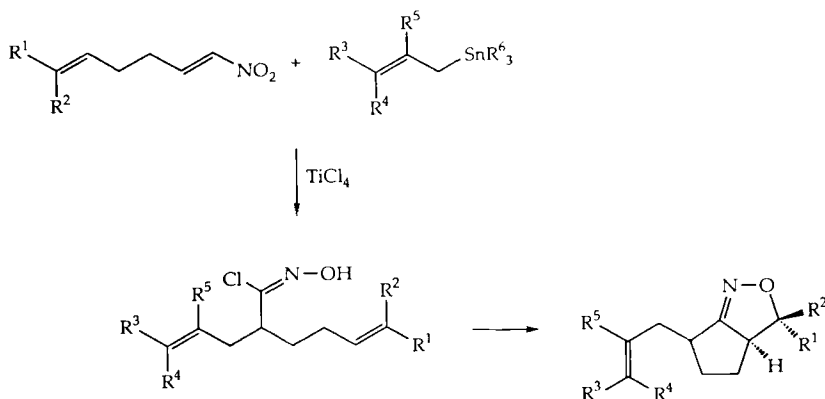
ester (18) (85JMC1109) or other standard methods to generate the nitrile oxide (19) (81TL3371; 83TL743) are preferable.

Nitroalkenes gave nitrile oxides by conjugate addition with *tert*-butyl isocyanide, followed by intramolecular rearrangement (Scheme 7) (87CC189), or by titanium tetrachloride-mediated conjugate addition of allylstannanes, followed by treatment with base (Scheme 8) [87S471; 89JCS(P1)289]. In each case conjugate addition is concomitant with nitrile oxide formation.

Nitrile oxides are generally unstable and readily undergo dimerization to give the corresponding oxadiazole *N*-oxides (Scheme 9), which are commonly referred to as furazans *N*-oxides or furoxans. Aryl nitrile oxides usually have a half-life of several hours, whereas aliphatic and acyl nitrile oxides are much more reactive. The dimerization of aryl nitrile oxides is retarded by electron-donating substituents and by bulky groups at the 2- and 6-positions (65JOC2809). Usually, only aryl nitrile oxides such as 2,4,6-trimethyl- and 2,6-dichloro-benzonitrile oxide are sufficiently unreactive to be stored (71M11); however, other nitrile oxides have been stabilized with tris-(4-bromophenyl)-aminium hexachloroantimonate (93TL4363). Interestingly, 4-methoxy-2,6-dimethylbenzonitrile oxide is



SCHEME 7



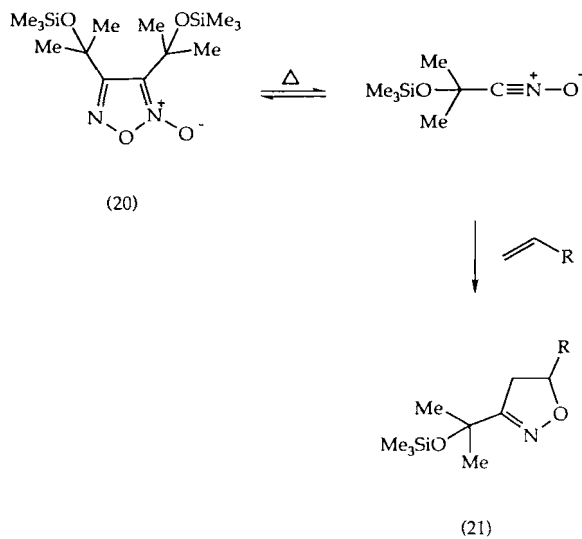
SCHEME 8

sufficiently stable that its structure has been determined through X-ray crystallographic analysis (68CC1409). To diminish competing dimerization, nitrile oxides are generally generated *in situ*, [63AG(E)565] in the presence of excess alkene. Low reaction temperatures and slow addition of reagents have also been used to control the rate of nitrile oxide formation [63AG(E)565; 71MI1]. In this manner, rearrangements of the nitrile oxides (71MI1) are also limited.

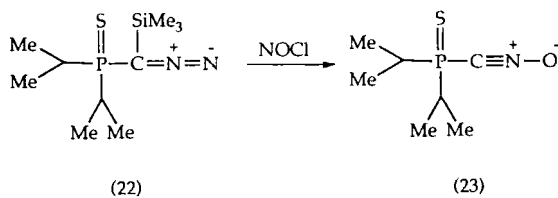
Cycloreversion of furoxans has also been used to generate nitrile oxides *in situ* under thermolytic conditions [72JCS(P1)1587; 76CC240; 79JCR(S)314, 79S36, 79TL2443; 81TL3371]. Of course, dimerization of nitrile oxides becomes inconsequential under these conditions but this procedure is limited by the tendency of nitrile oxides to rearrange to isocyanates, and by the cycloreversion of isoxazoline products, particularly at elevated temperatures [79AG(E)721; 85CB4203]. Curran and Fenk (85JA6023; 86TL4865) performed the thermolysis with bis-[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan (TOP-furoxan) (**20**) and a clean conversion to the isoxazolines (**21**) was observed (Scheme 10). Unprotected hydroxy groups on the alkene were shown to survive the procedure, which is not the case with the Mukaiyama method of nitrile oxide formation, and the cycloaddition with relatively unreactive alkenes proceeded in good yield.



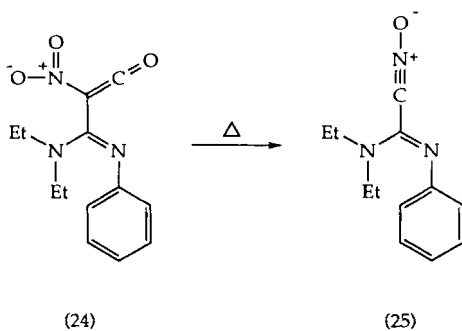
SCHEME 9



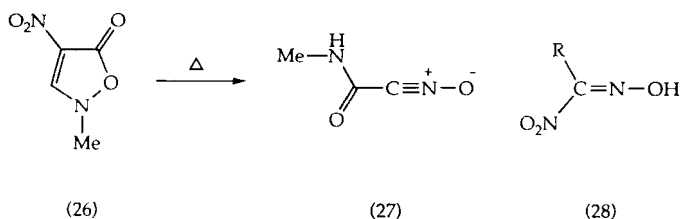
SCHEME 10



SCHEME 11



SCHEME 12

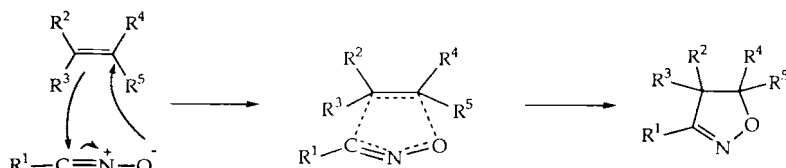


SCHEME 13

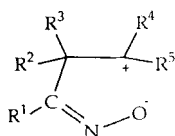
Nitrile oxides have also been identified in several mechanistic studies, although the synthetic utility of these procedures has yet to be examined. Reaction of the trimethylsilylated diazo compound (22) with nitrosyl chloride gave the nitrile oxide (23) (Scheme 11) (88AG289). The nitrile oxide (25) formed on thermolysis of the nitroketene (24) (Scheme 12) (92CC485). Heating the nitroisoxazolone (26) gave *N*-methylcarbamoylformonitrile oxide (27) (Scheme 13) [92H(34)1511]. Nitrile oxides were formed in reactions of arylsulfonyl halides with nitronate ions [88JCS(P2)725], through reactions of nitrolic acids (28) with base [91JCS(P2)249] and on treatment of substituted dinitromethane salts with dinitrogen tetroxide (92T6059).

III. Mechanism

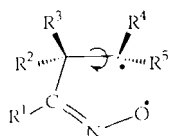
The reactions of nitrile oxides with alkenes are 1,3-dipolar cycloadditions and their mechanism has been the subject of numerous investigations. Apart from a one-step concerted mechanism (Scheme 14) (68JOC2291; 76JOC403), stepwise mechanisms proceeding via a zwitterionic intermediate (29) (71MI1) or via a diradical (30) (68JOC2285) have been proposed. Although there is no direct proof of any of these mechanistic possibilities, there is considerable evidence to suggest that the cyclic electron redistribution is substantially concerted. The configuration of the alkene is retained in the cycloadduct (76JOC403) and the reaction thermodynamics exhibit moderate enthalpy of activation and strongly negative entropy of activation, as expected for a concerted process. Solvent effects have been



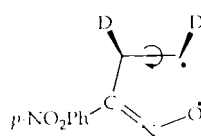
SCHEME 14



(29)



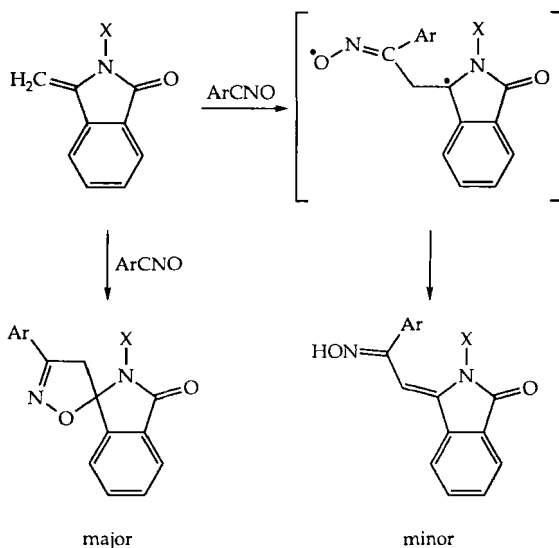
(30)



(31)

observed for cycloaddition reactions but these are regarded incompatible with the concept of highly polar intermediates (91BCJ3079). Instead they are likely to reflect aggregation of the reactants in solvents in which they have only limited solubility.

As mentioned above, the retention of configuration of the alkene in the cycloadduct is a compelling argument for the concerted mechanism (68JOC2291; 76JOC403) but this assumes that bond rotation in the putative diradical intermediate (30) is faster than cyclization (68JOC2285). In support of this assumption, Houk *et al.* (85JA7227) examined the stereoselectivity of the reactions of *cis*- and *trans*-1,2-dideuterioethylene with *p*-nitrobenzonitrile oxide. They calculated that the activation energy for isomerization of the diradical (31) would have to be 2.3 kcal mol⁻¹ higher than that for cyclization, which is contrary to expectation that the activation barrier for isomerization of the radical would be ≤ 0.4 kcal mol⁻¹—the cycloaddition would have a negative activation energy! There is evidence



SCHEME 15

to suggest, however, that the concerted process may be asynchronous [63AG(E)633; 90JOC4603], and a slower stepwise mechanism cannot be precluded (85JA7227). Diradical intermediates could account for the formation of oximes as by-products in some cycloaddition reactions (Scheme 15) (89JOC5012; 90JOC4603).

IV. Reactivity

Cycloaddition rates range over several orders of magnitude and to predict the likely success of a reaction, when alternative reaction pathways such as nitrile oxide dimerization are possible, it is necessary to understand the reactivity of the system.

The Sustmann frontier molecular orbital (FMO) theory (71TL2717; 74PAC569) has continued to be the basis used to rationalize reactivity (84JHC1397; 85JOC1278, 85MI1; 86JHC1539; 89JHC553; 90CCC2481; 91JHC605, 91M821). According to this model cycloadditions can be divided into three categories (Fig. 1), as follows:

Type I: The cycloaddition involves interaction between the highest occupied molecular orbital (HOMO) of the nitrile oxide and the lowest unoccupied molecular orbital (LUMO) of the olefin.

Type II: The reaction involves both the interaction between the HOMO of the nitrile oxide and the LUMO of the olefin and between the LUMO of the nitrile oxide and the HOMO of the olefin.

Type III: This is the opposite to Type I and involves interaction between the LUMO of the nitrile oxide and the HOMO of the olefin.

In each reaction category the reactivity is inversely proportional to the difference in energy between the interacting orbitals (69BCJ3399; 70FCF85). Electron-donating substituents raise the olefin's FMO energies,

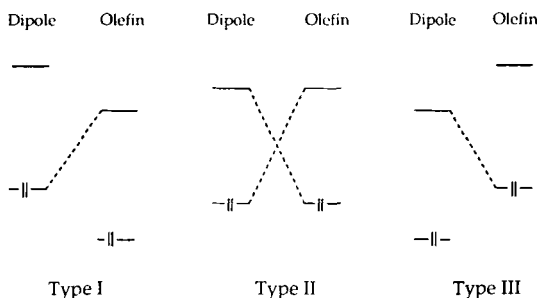


FIG. 1. Sustmann classification of the FMOs for the interaction of nitrile oxides with olefins.

decreasing the reactivity in Type I systems and increasing the reactivity in Type III systems. Conversely, electron-withdrawing substituents lower the olefin's FMO energies, increasing the reactivity in Type I systems and decreasing the reactivity in Type III systems. The effect of olefin substituents on Type II systems depends on which orbital interaction becomes dominant by substitution. With substituents of opposite types, each moderates the effect of the other. Conjugating substituents raise an olefin's HOMO and lower its LUMO, increasing the reactivity of Type I, Type II, and Type III systems. Accordingly, a carbonyl group increases the reactivity of an olefin. The effect of substituents on the nitrile oxide can be rationalized in a similar manner. Electron-donating substituents favor Type I reactivity, whereas electron-acceptor substituents increase the reactivity of Type III systems. Consequently Type III cycloaddition is favored with benzenesulfonyl and acyl nitrile oxides. The relative ease of dimerization of nitrile oxides is often used as a competitive standard to compare the reactivity of alkenes [84JCR(S)36, 84JCR(S)362, 84JHC1397] but this argument is simplistic, as it ignores the effect of the FMO energies of the nitrile oxides on reactivity (84BCJ1643). The utility of the Sustmann classification is widespread, particularly because substituent effects on FMO energies can often be estimated without the need for precise calculations.

Steric affects are not accommodated by the Sustmann classification. The steric effect of a single alkyl substituent on an alkene decreases reactivity, while the rate-enhancing effect of a conjugating substituent is greater than the retarding steric effect. The steric effect becomes dominant with more highly substituted olefins. With disubstituted alkenes the reactivity is generally retarded, more so with 1,2- than 1,1-disubstitution, although the electronic effects of both substituents still affect reactivity. *trans*-disubstituted alkenes are generally more reactive than the corresponding *cis*-isomers, presumably as a result of the greater steric compression of the *cis*-substituents during the cycloaddition [63AG(E)633]. Trisubstituted alkenes are even less reactive and steric effects dominate. Nitrile oxide dimerization is a particular problem in reactions of nitrile oxides with unreactive alkenes, such as unactivated di- and tri-substituted alkenes.

The degree of strain in cyclic olefins (62T3) and their ease of deformation to form cycloaddition transition states (80JA3951; 81JA2436, 81JA2438) also affect reactivity. Thus, for example, cyclopropenes (73TL1139; 74ZOR1669; 81S322; 90ZOR102), cyclobutenes [74JCS(P1)137; 76CC246; 85JOC1278], methylenecyclopropane (85CC1518), norbornene (62T3; 73LA2038), and benzvalene (86CB950) are highly reactive dipolarophiles. As expected, aromatic compounds such as benzene and naphthalene do not react with nitrile oxides (84MI1), due to the loss of resonance energy

that would accompany cycloaddition. Heteroaromatics undergo cycloaddition but at much reduced rates compared to those of their nonaromatic analogues. Accordingly, furan and thiophene are much less reactive than 2,3-dihydrofuran and 2,3-dihydrothiophene, respectively (84T441).

With 1-phenylsulfinyl- (85SC663), 1-fluoro- (90T7991), and 1,1-difluoro-substituted allenes (85MI1; 90T7991), the least substituted double bond reacts selectively. However, the α,β -bond of a nitrogen-substituted allene is the more reactive, presumably as a result of activation of that bond by the electron-donating substituent [90JCS(P1)533; 91JCS(P1)1843]. 1,3-Dienes follow the general trends, with the less substituted double bond reacting selectively [85T5569; 91JCS(P1)765; 92T6059], except in the case of some alkoxy-substituted dienes (88ZOR944) where the activating electronic effect of the alkoxy substituent balances the deactivating steric effect. With 1,2,3-trienes the terminal double bonds react selectively (86CB563).

As mentioned above, solvent effects have been observed for cycloaddition processes. Reactions of aryl nitrile oxides with substituted *p*-benzoquinones exhibited a 14-fold rate enhancement in water/ethanol (40:60) when compared with chloroform (91BCJ3079), presumably as a result of reactant aggregation in the water/ethanol mixture. Hydrogen bonding between nitrile oxides and hydroxyl- and amino-substituted alkenes increases reactivity, as does metal chelation of nitrile oxides and alkenes (92TL1357; 93TL4011). It has also been reported that cycloaddition reactions can be accelerated significantly by the use of ultrasound (91TL4171) and are catalyzed by baker's yeast (90TL899). The rates of reactions of nitrile oxides with alkenes are decreased by adding Lewis acids, presumably because the nitrile oxides are good Lewis bases and complexation effectively inhibits cycloaddition (87JOC2137).

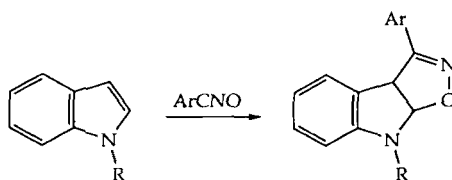
V. Regioselectivity

With unsymmetrical olefins, the direction of addition of the nitrile oxide must be considered. Monosubstituted alkenes afford 5-substituted isoxazolines almost exclusively, regardless of the electron-withdrawing or -donating nature of the substituent. This trend was studied by Martin and Dupré (83TL1337) and is illustrated by numerous examples [86CL183; 87JHC701, 87S998; 88KGS1034; 89JHC255, 89JOC3073, 89SC2237, 89ZOR1901; 90CCC2481, 90CJC1271, 90JHC557, 90JOC283, 90KGS1250, 90MI2, 90T1975; 91ACS736, 91BCJ375, 91JCS(P1)2801, 91JOC1812, 91MI2, 91TL683, 91TL4171; 92CC939, 92TL6811; 93TL2831, 93TL3169]. In the majority of cases with 1,1-disubstituted and trisubstituted olefins,

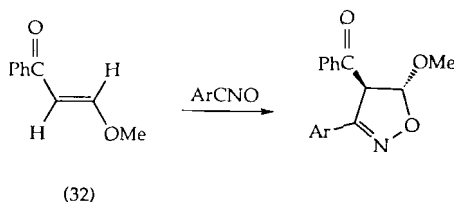
the oxygen of the nitrile oxide becomes attached to the more sterically hindered end of the double bond [84JHC1121; 85JOC903, 85JOC1278; 86LA1863; 87H755; 89CC986; 89JOC5585, 89JOC5883, 89TL1477; 90JCR(S)202, 90JHC2097, 90JOC3045, 90JOC4603, 90JOC4732, 90LA1097, 90ZOR1274; 91JCR(S)81, 91JHC605, 91JHC1945, 91M821; 92BCJ2484, 92H(34)1703, 92JIC282; 92LA591, 92T6059, 92TL4879].

A mixture of regioisomers is usually obtained with 1,2-disubstituted alkenes and where they are reactive, tetrasubstituted alkenes, although electron-donating amino (86BCJ3631; 89JOC5585; 90JHC1931), alkoxy (84T441), and alkylthiyl (84T441) substituents tend to orientate the cycloaddition such that they are at the 5-position in the cycloadducts. Consistent with this trend, indole and its *N*-substituted derivatives react mainly as shown in Scheme 16 but electron-withdrawing substituents on the indole nitrogen reduce the regioselectivity of the cycloaddition, presumably as a result of reduced polarization of the double bond [84JCR(S)36]. Acyl (85TL4105; 86CL1925, 86JHC1681; 87CCC1315; 91BCJ3274, 91M165; 92T8053) and sulfinyl (91TL3699) substituents direct the oxygen of the nitrile oxide such that they are at the 4-position of the cycloadduct. The combined effects of the alkoxy and acyl substituents resulted in the highly regioselective addition of nitrile oxides to the 1,2-disubstituted alkene (**32**) (Scheme 17) (91JHC429), while the substituents of the uracil (**33**) acted in a similar manner (Scheme 18) (92JOC1088). Reaction of benzonitrile oxide (**3**) with the allylic alcohol (**34**) in the presence of *n*-butoxymagnesium bromide, to give the isoxazolines (**35**) and (**36**) (Scheme 19) in the ratio 99 : 1, can be attributed to metal chelation in the transition state (Fig. 2) (92TL1357) and indicates the potential of this approach in the control of regioselectivity of cycloadditions. β -Cyclodextrin was also used to control the regioselectivity of cycloadditions (90TL899; 92PAC1141).

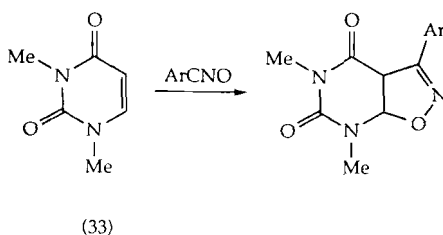
The reaction of (**37**) with (**38**) to give (**39**) (Scheme 20) in high yield is a good example of exploitation of alkene reactivity and regioselectivity in synthesis (88TL1307). Only the monosubstituted double bond reacts, with the nitrile oxide oxygen adding to the most hindered end of that double bond. The regioselectivity of nitrile oxide cycloadditions with dipo-



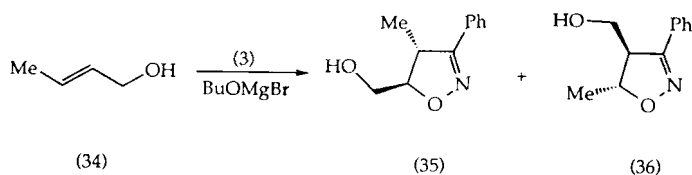
SCHEME 16



SCHEME 17



SCHEME 18



SCHEME 19

larophiles such as methylenecyclopropane (85CC1518; 86CC813; 88JOC2426; 92JOC4206, 92T3323; 93M11), analogues with electron-withdrawing substituents on the methylene group (87TL3845) or with ring substituents (88JOC2426; 91CB1619; 92JOC4206), and methylenecyclobutane and its derivatives (92T5283) is consistent with the guidelines outlined above, but alkylidene and arylidene cyclopropanes show an unexplained tendency for the cyclopropyl substituent to be at C-4 in the product isoxazoline (87TL3845; 92T3323; 93M11). In other rare cases the nitrile oxide

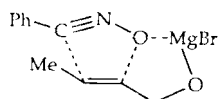
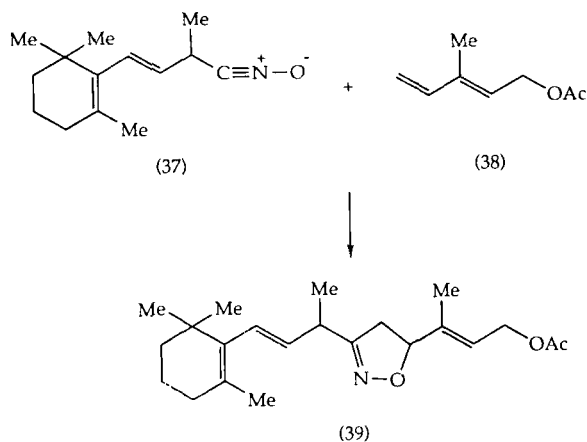


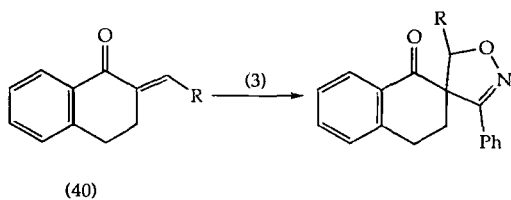
FIG. 2. Metal chelation in the transition state of the cycloaddition of benzonitrile oxide (3) with (*E*)-2-butenol.



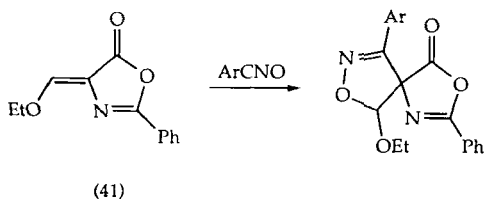
SCHEME 20

oxygen bonds to the less hindered carbon of the alkene. Apparently this was the case in reactions of the ketones (40) (Scheme 21) (86JIC1002). The regioselective reaction of the oxazolone (41) (Scheme 22) (92JHC251) can be attributed to the dominance of electronic factors over steric effects.

With 1-phenylsulfinylallene, the residual double bond is found mainly at the 5-position in the cycloadduct (85SC663), whereas nitrogen-substituted allenes afford mainly 4-methylene-substituted isoxazolines [90JCS(P1)533; 91JCS(P1)1843]. The regioselectivity of addition to 1-fluoro- and 1,1-difluoro-allene depends on the nitrile oxide and is thought to reflect the



SCHEME 21



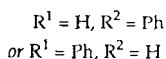
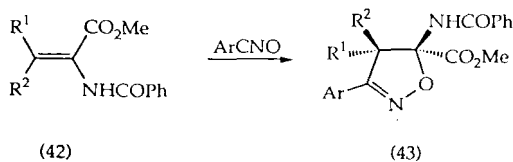
SCHEME 22

extent of electrostatic repulsion between the reactants (85MI1; 90T7991). The nitrile oxide oxygen reacts at C-2 of 1,3-butadienes [85T5569; 88ZOR944; 91JCS(P1)765] and at C-1 and C-4 of tetrasubstituted 1,2,3-trienes (86CB563).

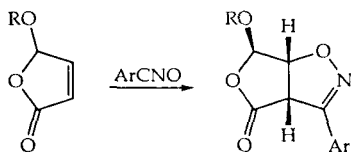
VI. Stereoselectivity

Aspects of the stereoselectivity of nitrile oxide cycloaddition reactions have been reviewed (89G253). The most obvious stereochemical consequence of the cycloaddition is that the configuration of the alkene is retained in the product isoxazoline and this feature continues to be exploited in asymmetric synthesis. For example, the dehydrophenylalanine derivatives (**42**) gave the corresponding isoxazolines (**43**), stereospecifically (Scheme 23) (91JHC1945).

When the faces of the alkene are nonequivalent, reactions often display considerable diastereoselectivity. This is particularly apparent in cyclic systems (88CC1339; 89JOC2209; 90BCJ3300; 92T8053). The stereoselectivity is highly sensitive to steric factors, as illustrated in the *anti*-addition of nitrile oxides to 5-alkoxy- and 5-acyloxy-2(*5H*)-furanones (Scheme 24) (87CCC1315; 91M165). In contrast, the hydroxyfuranone (**44a**) and the corresponding lactam (**44b**) gave approximately equal quantities of the products of *syn*- and *anti*-addition (Scheme 25) (87CCC1315). Since there was no interconversion of the isomers of the cycloadducts under the reaction conditions, the stereoselectivity must occur in the cycloaddition and presumably results from a balance of hydrogen bonding, between benzonitrile oxide (**3**) and the alkenes (**44**), and steric interactions. Similar effects have been observed in reactions of 3-substituted cyclopentenones, where nitrile oxides generally add to the *anti* face (75TL3543; 78JA105). Hydrogen bonding between the nitrile oxide and the alkene can also outweigh these steric effects, however, such that 3-hydroxycyclopentene (74TL229) and, to a greater extent, the cyclopentenyl amides (**45**) react



SCHEME 23



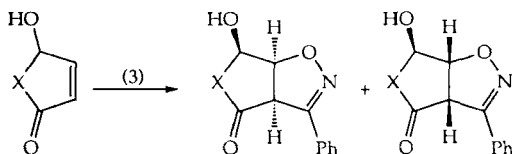
R = alkyl or acyl

SCHEME 24

by *syn* addition (Scheme 26) with a high degree of regioselectivity (90JOC3710).

2-substituted methylenecyclopropanes react by *anti*-addition with a high degree of stereoselectivity (Scheme 27) (88JOC2426, 88JOC2430; 90JOC1762; 93MI1), but analogous methylenecyclobutanes show little diastereoselectivity in their reactions (92T5283). This can be attributed to the greater flexibility of the cyclobutane ring, which can adopt a conformation where there are minimal steric interactions between the substituent and the incoming nitrile oxide.

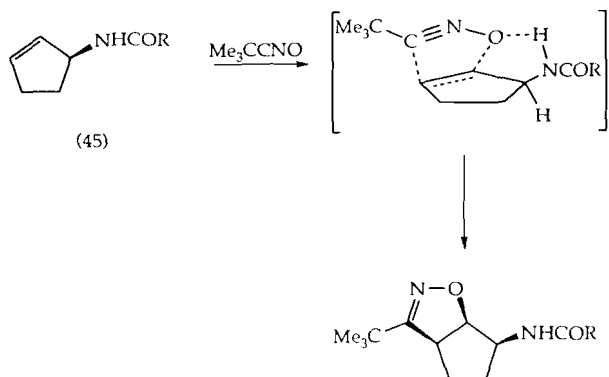
The diastereoselectivity is generally less with acyclic than cyclic alkenes. A number of groups have reported modestly diastereoselective nitrile oxide cycloadditions to chiral allyl ethers and alcohols (Scheme 28) [74JCS(P1)137, 74TL229; 76CC246; 78JA105; 81JCS(P1)3048; 82JA5788, 82TL4563; 83T2247, 83TL5501; 84JOC4674]. Reactions slightly favor the *syn* isomer for allyl alcohols ($R^1 = H$) and, to a greater extent, the *anti* isomer for allyl ethers ($R^1 = \text{alkyl, aryl}$). Houk *et al.* (84JA3880) combined experimental results and theoretical studies to rationalize this stereoselectivity in terms of a preferred conformation of the transition state (Fig. 3), in which alkyl substituents at the chiral center prefer the sterically less crowded "anti" conformation, an allylic hydroxyl group prefers the "outside" position to maximize hydrogen bonding with the nitrile oxide oxygen, and an ether prefers the "inside" conformation, due to secondary orbital interactions. This concept has been subsequently referred to as



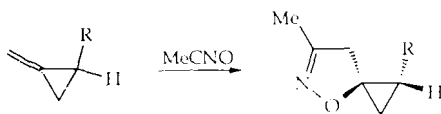
(44)

a) X = O
b) X = NH

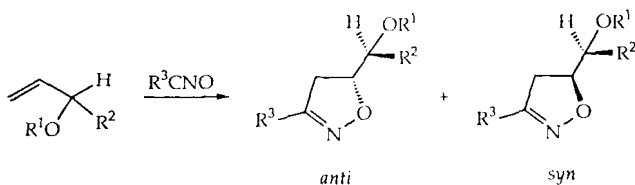
SCHEME 25



SCHEME 26



SCHEME 27



SCHEME 28

the “inside alkoxy” effect. In later studies where the groups attached to the stereogenic centre varied only in size (Scheme 29), it was determined that the largest group (L) assumed the “anti” position, the medium-sized group (M) the “inside” position, and the smallest group (S) the “outside” position, as a result of steric interactions (86JA2754). It follows that the

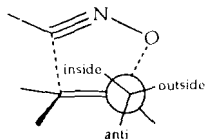
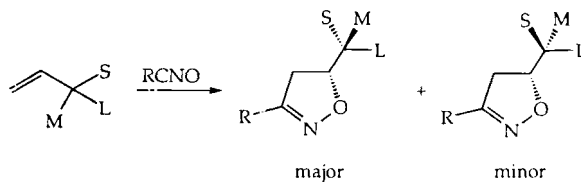


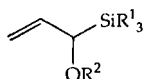
FIG. 3. Houk's “inside alkoxy” model for the reaction of nitrile oxides with chiral allylic alcohols and ethers.



SCHEME 29

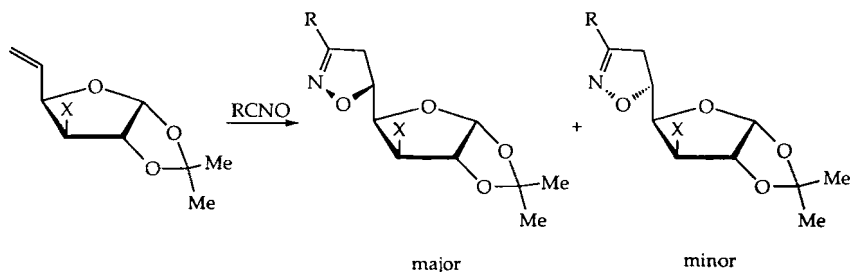
“inside alkoxy” effect is a combination of steric repulsion and secondary orbital interactions (86JA2754).

Houk’s model has been used to account for diastereoselectivity observed in nitrile oxide cycloadditions with the (α -oxyallyl)silanes (**46**) (88T3945). The direction and magnitude of asymmetric induction was

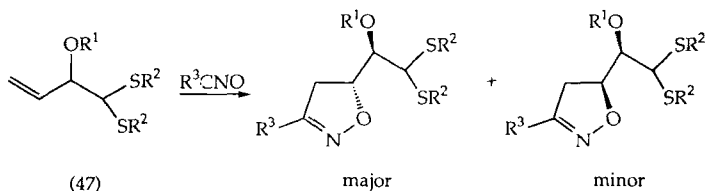


(46)

found to depend on the allylic oxygen substituent. It was found that a free hydroxy substituent provided a modest excess of the *syn* diastereomer, silyl ethers showed modest to good selectivity for the *anti* diastereomer, and various acyl derivatives showed low diastereoselectivity. The diastereoselectivity observed in reactions of unsaturated sugars (Scheme 30) (89JOC793; 91CCC132, 91MI2; 93TL2831) has also been rationalized in terms of the “inside alkoxy” effect (89JOC793). Interestingly, the *syn* selectivity in reactions of chiral allyl alcohols with nitrile oxides was increased through metal chelation of the reactants (91TL6367). Reactions of chiral allyl ethers (**47**) derived from 1,1-dithio-3-buten-2-ols displayed consistently high (>10:1) diastereoselectivity (Scheme 31), presumably as a result of the “inside alkoxy” effect and steric interactions associated with the bulky dithioacetal moiety (88T4645).



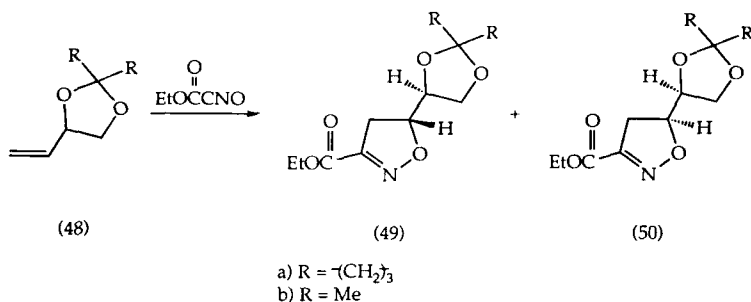
SCHEME 30



SCHEME 31

Diastereoselective reactions of the dioxolanes (**48**) have been reported by several groups (84ACR410, 84JOC2762, 84T2199; 85JOC778; 90S556, 90T1975; 92JOC2825). For example, the dioxolane (**48b**) gave the adducts (**49b**) and (**50b**) in the ratio 4 : 1 (Scheme 32) (84JOC2762). The diastereoselectivity has been rationalized in terms of the Felkin-Anh (80M11; 82JA1106; 83TL2231) transition state model, as illustrated in Fig. 4 (84JOC2762), but the results are also consistent with Houk's model. Reactions of the silyl ether (**51**) (Scheme 33) have also been discussed (84JOC2762) in terms of the Felkin-Anh model but are better accommodated using the "inside alkoxy" theory.

Encouraged by the stereoselectivity observed in nitrile oxide cycloadditions to the dioxolanes (**48**), Wade *et al.* (84T601) studied reactions of



SCHEME 32

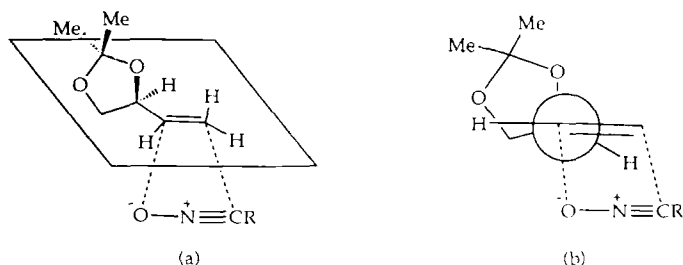
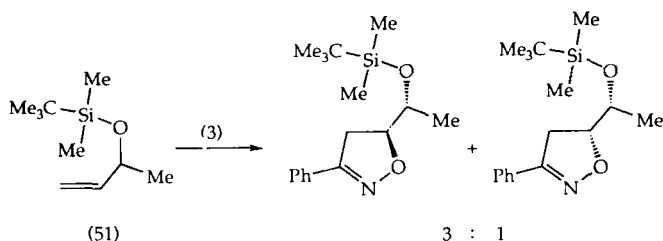
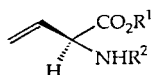


FIG. 4. Houk's transition state model (a) and the Felkin-Anh transition state model (b) for the reaction of the dioxolane (**48**) with nitrile oxides.



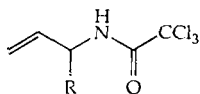
SCHEME 33

derivatives of vinylglycine (**52a**) but the diastereoselectivity was generally poor, ranging from 0 to 40% diastereomeric excess. Similar results were reported by Fushiya *et al.* (87CL2229), for reaction of the vinylglycine derivative (**52b**) with acetonitrile oxide, whereas the cyclic vinylglycine derivative (**53**) gave mainly the diastereomer (**54**) on treatment with nitrile oxides (Scheme 34) (92M11). Halling *et al.* (91ACS736) reported little stereoselectivity in the cycloaddition of chloronitrile oxide to the *N*-allyltrichloroacetamides (**55**). Curran and Kim (86S312) observed that cycloaddition of benzonitrile oxide (**3**) with the (α -methylallyl)silane (**56**) also occurred with only poor selectivity (Scheme 35). Methylphenylvinylphosphine oxide (**57**) gave cycloadducts with approximately 40% diastereomeric excess (Scheme 36) (89JOC3073). The diphenylphosphine oxide (**58**) reacted with nitrile oxides to give mainly the *anti*-cycloadducts (**59**) (Scheme 37), consistent with Houk's transition state model (91TL4171). Recently, (*S*)-1-(2-naphthyl)ethyl vinyl ether was shown to react with nitrile oxides with a modest degree of diastereoselectivity [93JCS (P1)1277].



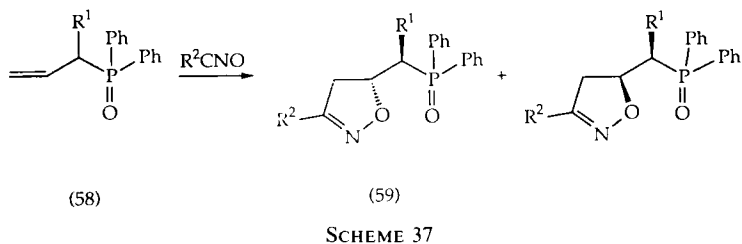
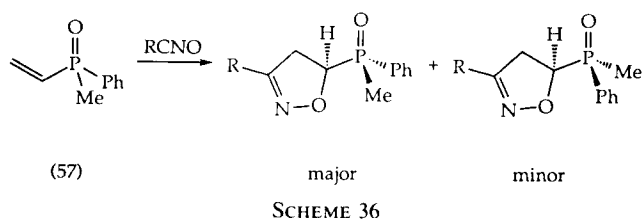
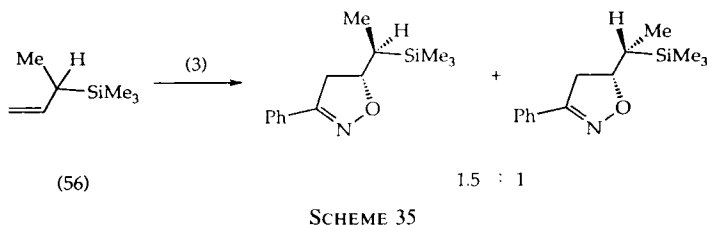
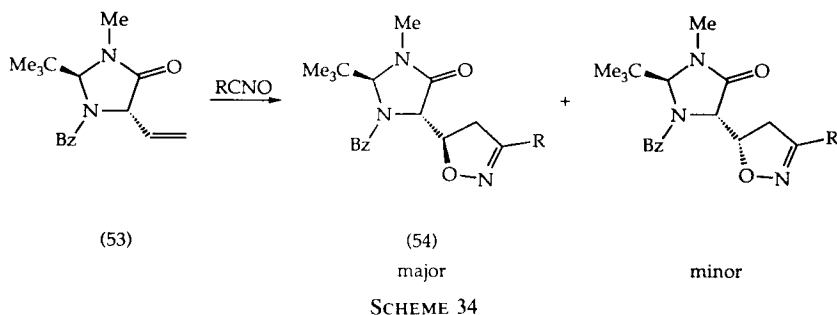
(52)

- a) $\text{R}^1 = \text{R}^2 = \text{H}$
 b) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{OCOPh}$

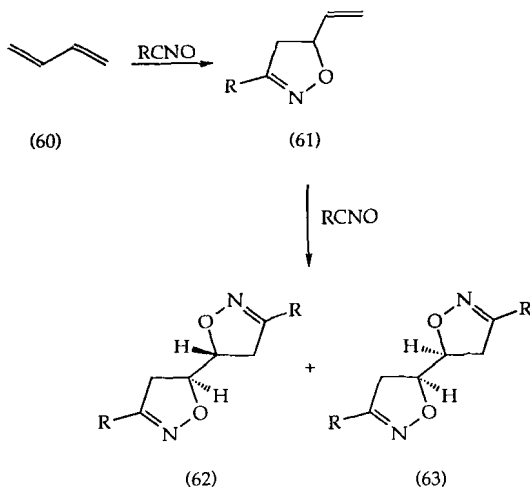


(55)

- a) $\text{R} = \text{CH}(\text{Me})\text{Et}$
 b) $\text{R} = \text{Ph}$



Reactions of vinylisoxazolines have also been studied. In reactions of 1,3-butadiene (**60**) with nitrile oxides, the *erythro* adducts (**62**) were formed in preference to the corresponding *threo* isomers (**63**) (Scheme 38) (83T2247; 85T5569), the isomer ratios ranging from 2.7:1 to 6.7:1. The

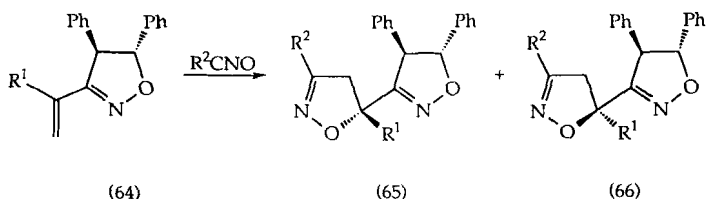


SCHEME 38

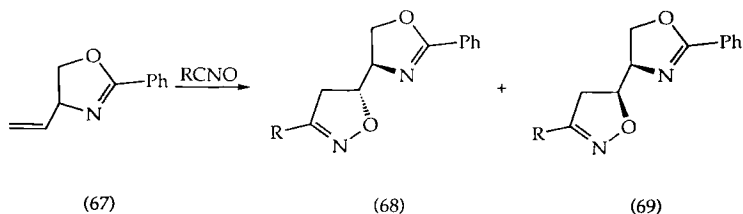
isomer ratios reflect the diastereoselectivity of nitrile oxide addition to the 5-vinylisoxazolines (**61**). The 3-vinylisoxazolines (**64**) gave the cycloadducts (**65**) and (**66**) with diastereomeric excesses ranging from 10 to 45% (Scheme 39) (90JOC3045).

The 4-vinylisoxazoline (**67**) and the 4-vinylisoxazolidine (**70**) gave mixtures of the isoxazolines (**68**) and (**69**), and (**71**) and (**72**), respectively, in which the *erythro* products (**69**) and (**72**) were formed in 32–64% diastereomeric excess (Schemes 40 and 41) (93TL3169). The results were interpreted by analogy with the “inside alkoxy” effect. Reactions of the acyclic analogue (**73**) were less stereoselective and favored the *threo* cycloadducts (**74**). The reversed selectivity was attributed to hydrogen bonding between the oxygen of the nitrile oxide and the hydroxy substituent of the alkene (**73**) (93TL3169).

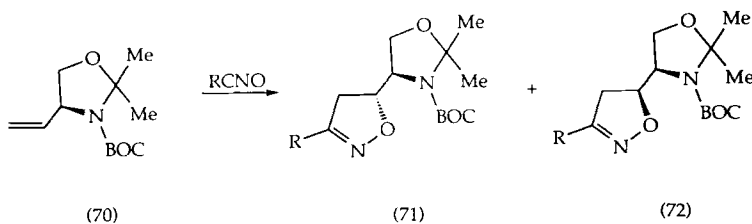
Whereas the studies described above involve reactions of chiral alkenes with achiral nitrile oxides, the stereoselectivity of reactions of chiral nitrile oxides has also been studied. The nitrile oxide (**75**) reacted with *cis*-but-



SCHEME 39

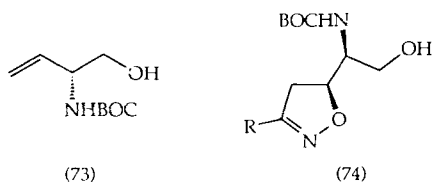


SCHEME 40

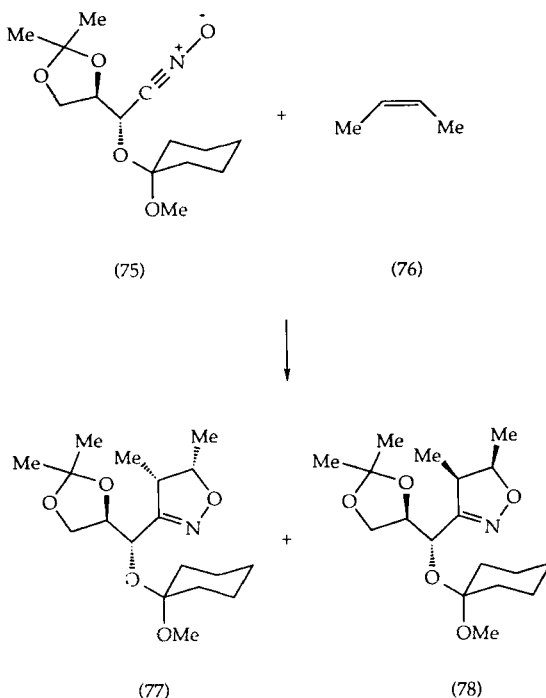


SCHEME 41

2-ene (**76**) to give a 2.9 : 1 mixture of the isoxazolines (**77**) and (**78**) (Scheme 42) (83CC1460). *trans*-But-2-ene and cyclopentene also reacted stereoselectively but styrene (**80**) and vinylcyclohexane did not, indicating that stereocontrol derives from the interaction between the chiral auxiliary and the substituent at C4 of the developing isoxazoline. By a similar argument, the low stereoselectivity reported for the reaction of the chiral oxazoline (**79**) with styrene (**80**) (Scheme 43) is not surprising (93TL3169). The dioxolanes (**81**) reacted with dimethyl maleate and cyclopentene with modest diastereoselectivity but reactions with styrene and dimethyl fumarate gave equal mixtures of diastereomeric cycloadducts (84T177). The bislactim ether (**82**) reacted with alkenes without stereocontrol (92T5607).



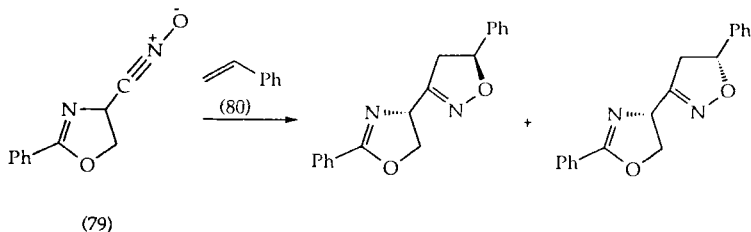
The homochiral nitrile oxide (**83**) reacted with the chiral dioxolane (*R*)-(**48b**) to give the cycloadducts (**84**) and (**85**) as a 4 : 1 mixture (Scheme 44). The degree of diastereoselectivity was similar to that observed in reactions of the dioxolanes (**48**) with achiral nitrile oxides, indicating that the chirality of the nitrile oxide (**83**) had little effect on the stereochemical course of the reaction (84JOC2762). A similar conclusion was reached to



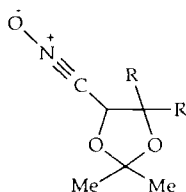
SCHEME 42

explain the diastereoselectivity in the synthesis of the isoxazolines (**87**) (Scheme 45), as the reaction of the nitrile oxide (**86**) with butyl allyl ether was much less stereoselective (87TL3189). The dioxolane (**88**) has been used in the synthesis of sugars (Scheme 46), but again the diastereocontrol most likely derives from the dipolarophile (**89**) (91CC132, 91MI2; 93TL2831).

The approach of using chiral auxiliaries to control stereoselectivity has been investigated by a number of groups. Curran *et al.* (89JA9238) noted that development of chiral auxiliaries in these systems is a particular

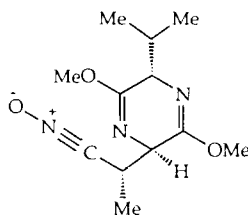


SCHEME 43



(81)

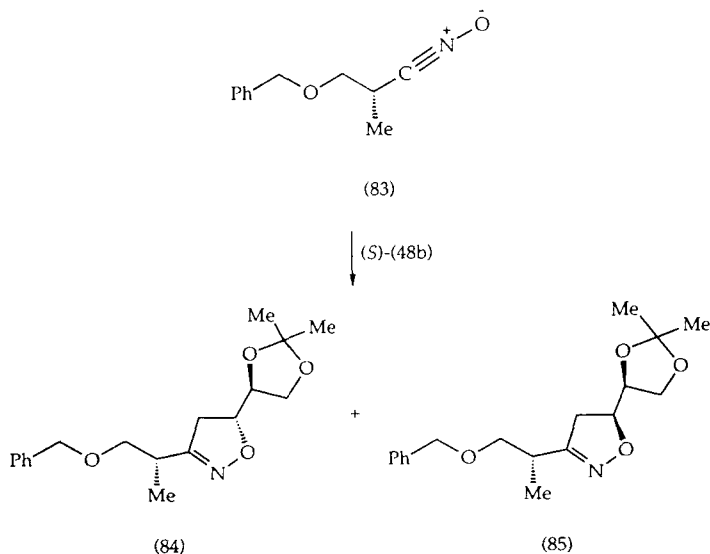
a) R = H
b) R = Me



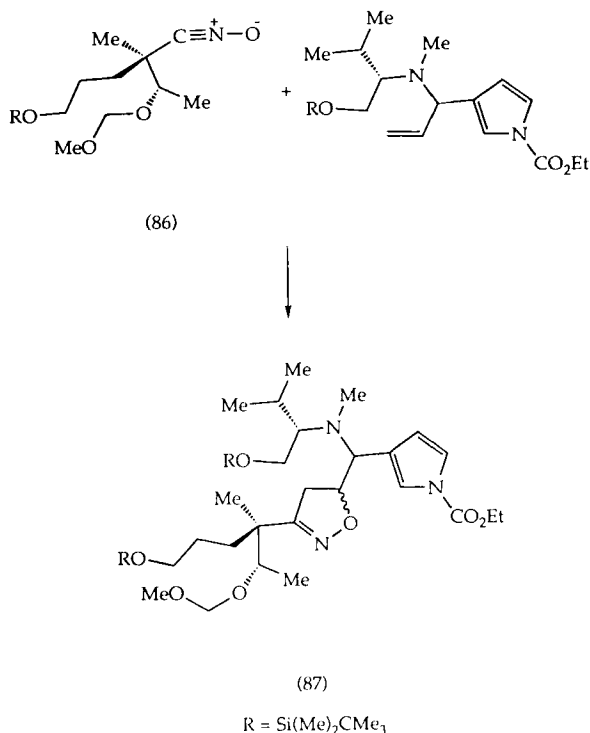
(82)

challenge because the geometry of the transition state limits their effects. Although asymmetric induction can be enhanced in other cycloaddition reactions by using Lewis acid catalysts, this option is not available in nitrile oxide cycloadditions because the nitrile oxides act as Lewis bases.

Reactions of *p*-nitrobenzonitrile oxide with the menthyl acrylate (**90a**), the corresponding menthyl allyl ether (**90b**), and the acrylate (**91**) gave adducts with less than 10% diastereoselectivity (84TL2191; 87JOC2137). Reactions of the sulfonamides (**92**) were more stereoselective and that of the dicyclohexyl derivative (**92b**) with benzonitrile oxide (**3**) gave the diastereomers (**93b**) and (**94b**) (Scheme 47) in a ratio of ca. 4:1 (87JOC2137). The bornyl crotonates (**95a**) gave only *trans*-4,5-substituted cycloadducts and mainly the regioisomers (**96a**) (Scheme 48) with diaste-



SCHEME 44

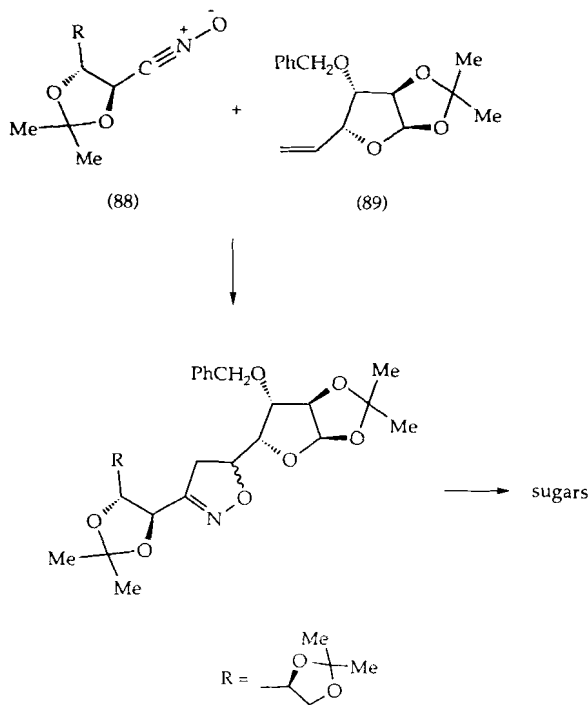


SCHEME 45

reomeric excesses ranging from 5% (R^1 = naphthyl, R^3 = Ph) to 54% (R^1 = Ph, R^3 = Me) (88JOC2468). The stereoselectivity of formation of the minor regioisomers (**97a**) was generally greater and ranged from 12% (R^1 = H, R^3 = Ph) to 80% (R^1 = naphthyl, R^3 = Ph). The bornyl acrylates (**95b**) reacted regioselectively, as expected, with a degree of stereoselectivity similar to that for the reactions of the crotonates (**95a**) (90T2473). The esters (**96**) and (**97**) were easily cleaved and the chiral auxiliaries retrieved.

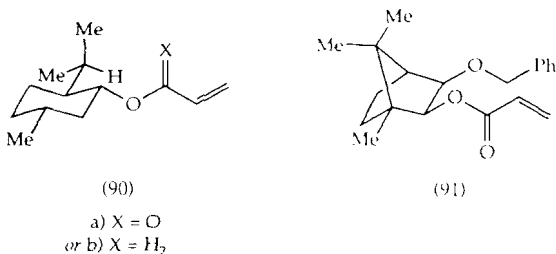
Acryloyl esters bearing *chiro*-inositol derivatives as chiral auxiliaries reacted with a consistently high degree of stereoselectivity (92TL5763). For example, the *tert*-butyldiphenylsilyl ether (**98**) reacted with benzonitrile oxide (**3**) to give the cycloadduct (**99**) in 90% diastereomeric excess (Scheme 49). The stereochemical outcome of the reaction indicates *si*-face attack to the *s-cis* conformer of the acrylate (**98**). The chiral auxiliary was recovered after treatment of the isoxazoline (**99**) with L-Selectride.

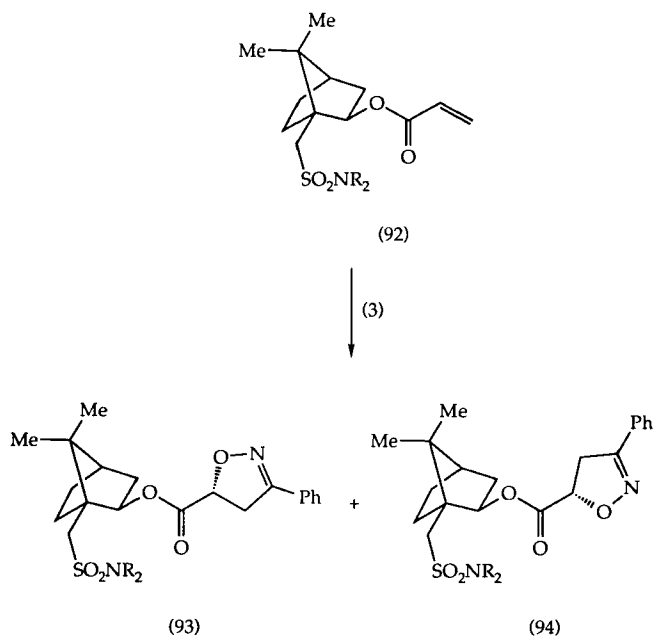
Reactions of the Oppolzer's chiral sultam derivative (**100a**) with nitrile oxides showed considerable diastereoselectivity [88TL3555; 90JOC4585;



SCHEME 46

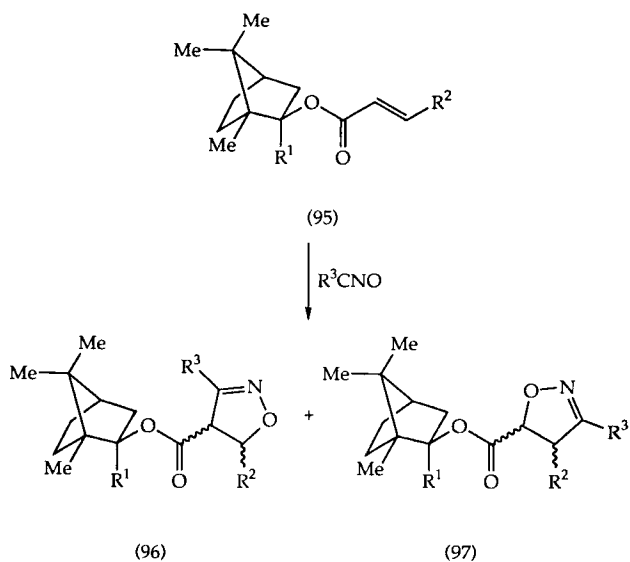
91JCS(P1)2627; 92TL6811]. For example, the cycloadduct (**101a**) was obtained in 90% diastereomeric excess (Scheme 50) (88TL3555). The stereoselectivity is consistent with reaction of *tert*-butylnitrile oxide with the *s-cis* conformation of the sultam (**100a**). The α -methacryloyl sultam (**100b**) was less reactive than the acrylamide (**100a**) and its reactions showed less stereoselectivity, whereas reactions of the crotonyl sultam (**100c**) displayed stereoselectivity analogous to that of the acrylamide (**100a**), but afforded mixtures of regioisomers (90JOC4585). The greater selectivity in the reactions of the sultam (**100a**) compared to that for reactions of esters





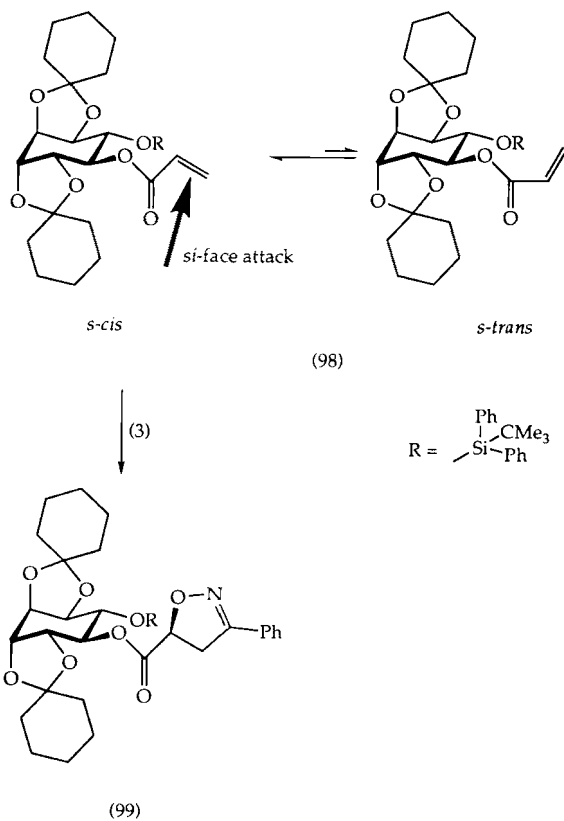
a) R = CHMe₂
b) R = cyclohexyl

SCHEME 47

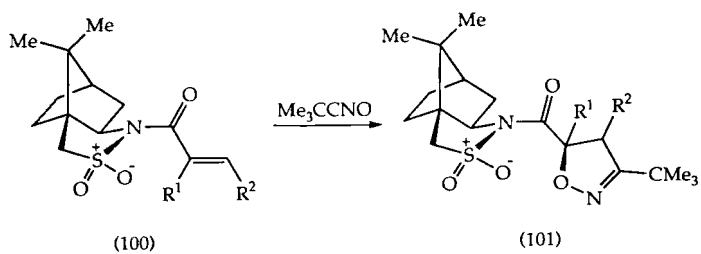


a) R² = Me
b) R² = H

SCHEME 48



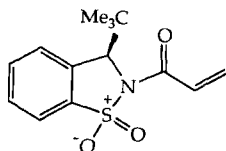
SCHEME 49



- a) $\text{R}^1 = \text{R}^2 = \text{H}$
 b) $\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}$
 c) $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}$

SCHEME 50

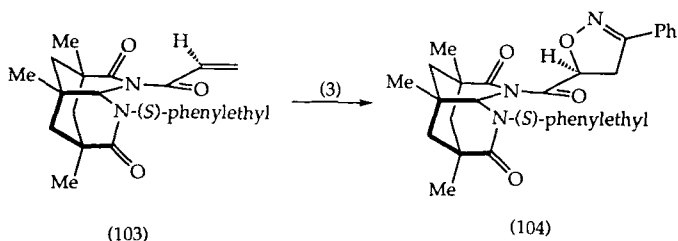
described above is consistent with a greater conformational preference of the sultam (**100a**) (88TL3555). Oppolzer *et al.* (91TL4893) reported the synthesis of the acryloyl sultam (**102**) and its enantiomer. Their reactions with nitrile oxides proceeded stereoselectively, with the ratios of diastereomeric products ranging from 95 : 5 to 98 : 2.



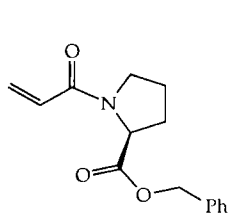
(102)

Even greater stereoselectivity was obtained using derivatives of Kemp's triacid (81JOC5140) as chiral auxiliaries. Accordingly the chiral acrylimide (**103**) gave the corresponding isoxazoline (**104**) (Scheme 51) in greater than 98% diastereomeric excess (89JA9238; 93T995). A diastereomer of the imide (**103**) was used to reverse the stereocontrol (89JA9238; 93T995). The *N*-acryloylproline derivative (**105**) reacted with nitrile oxides to give isoxazolines in diastereomeric ratios of ca. 3 : 1 (90LA1013). The chiral auxiliaries of the bis-proline derivative (**106**) displayed synergistic stereocontrol and gave 9:1 mixtures of diastereomers of cycloadducts (90LA1013).

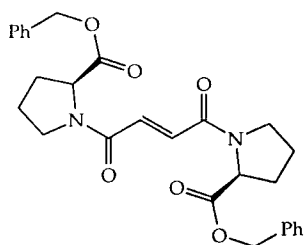
The imidazolines (**107**) and (**108**) reacted with nitrile oxides with modest to high stereoselectivity, but low regioselectivity (91BCJ3274). Diastereoselective reactions of the oxazolidines (**109**) and the imidazoline (**110**) have also been reported (91BCJ3274, 91TA1185). As a representative example, the imidazoline (**110**) reacted with benzonitrile oxide (**3**) at room temperature to give the adducts (**111**) and (**112**) in the ratio 4 : 1. After separation



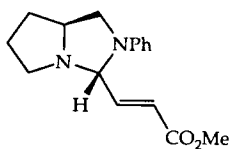
SCHEME 51



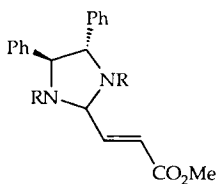
(105)



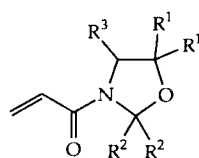
(106)



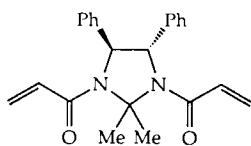
(107)



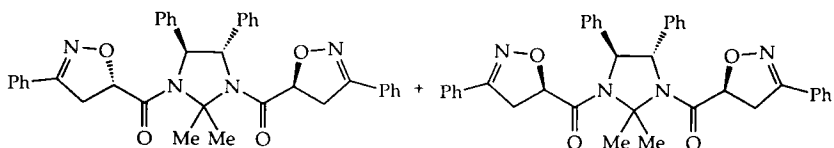
(108)



(109)

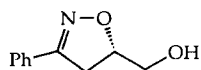
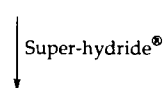
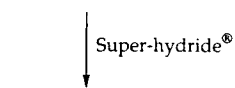


(110)

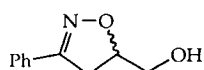


(111)

(112)



(113)



(114)

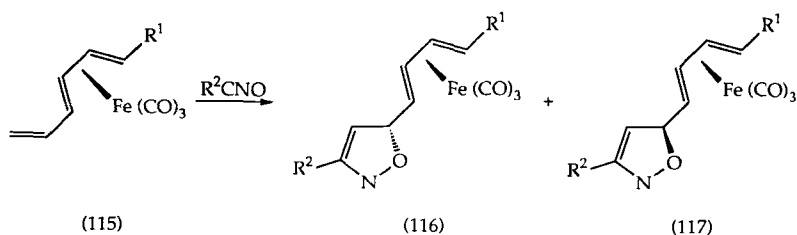
SCHEME 52

and reduction with lithium triethylborohydride, the adduct (**111**) gave the homochiral alcohol (**113**), while the diastereomer (**112**) gave the corresponding racemate (**114**) (Scheme 52).

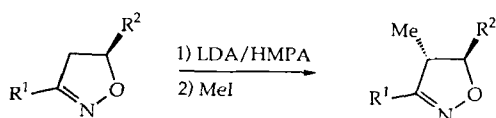
Another method used in the diastereoselective synthesis of isoxazolines involved reactions of the iron complexed trienes (**115**) with nitrile oxides to give the cycloadducts (**116**) and (**117**) in a ratio of ca. 9:1 (Scheme 53) (89TL6517). There have been reports on the use of baker's yeast in the enantioselective synthesis of isoxazolines from 4-vinylpyridine and aryl nitrile oxides, and of the enhancement of that selectivity using β -cyclodextrin (90TL3201; 92PAC1141).

Stereocontrolled modification of isoxazolines provides an alternative to their stereoselective synthesis. For example, alkylation of 5-substituted isoxazolines afforded only the *trans*-4,5-substituted isomers (Scheme 54) (84JOC2762). Conceptually these isoxazolines are accessible from *trans*-1,2-disubstituted alkenes but reactions of that type are complicated by a lack of regioselectivity. Alkylation of 3,4,5-substituted isoxazolines occurred on the 3-substituent with a high degree of regioselectivity (84JOC2762) and modest to good stereoselectivity (87JA3036; 90SC3575, 90T7325), as illustrated in reactions of the 3-ethyl-substituted isoxazoline (**118**) where the electrophile added opposite the 4-substituent (Scheme 55). Hydroxylation of the isoxazoline (**119**) gave only the alcohol (**120**) (Scheme 56) (90S556).

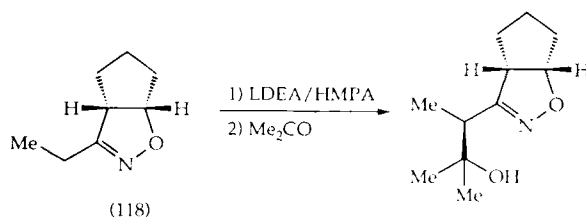
Reactions of the 5-acylisoxazolines (**121**) with *L*-Selectride were highly stereoselective and gave mainly the *syn*-5-(α -hydroxyethyl)isoxazolines (**122**) (Scheme 57) [91JCS(P1)2613]. Yeast reduction of racemic 5-acetyl isoxazolines gave the diastereomeric alcohols (**123**) and (**124**), each



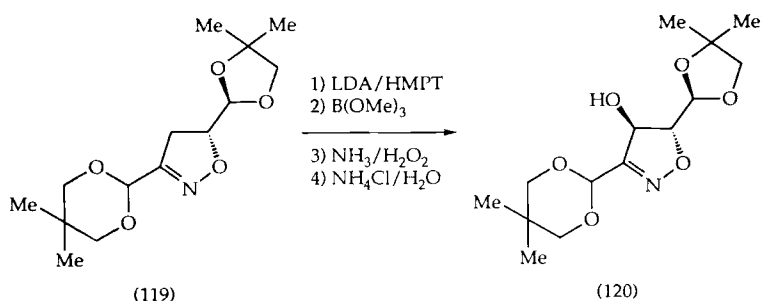
SCHEME 53



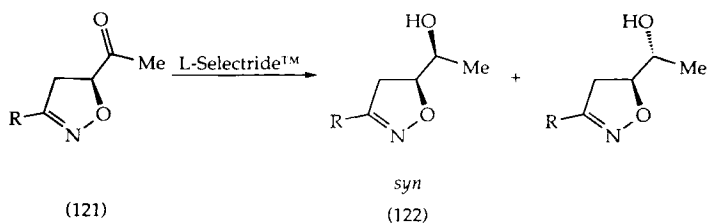
SCHEME 54



SCHEME 55

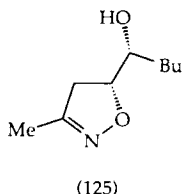
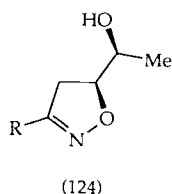
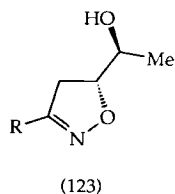


SCHEME 56



SCHEME 57

in 97–98% enantiomeric excess (88TL6167; 89LA1257). With Grignard reagents, 5-acyl- and 5-formyl-isoxazolines reacted stereoselectively, according to a conformation determined by metal chelation for the former (Fig. 5) and a Felkin–Anh model in the latter (Fig. 6) [91JCS(P1)2613]. This approach has been used in conjunction with the achiral synthesis of



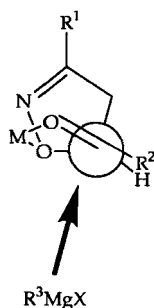


FIG. 5. Metal chelation in Grignard addition to 5-acyl-2-isoxazolines.

isoxazolines from the sultam (**100a**), to obtain the alcohol (**125**) as a single enantiomer [91JCS(P1)2627].

Oxidation of the furoisoxazolines (**127**) with *m*-chloroperbenzoic acid in methanol to give the hydroxyethers (**128**) and with osmium tetroxide to give the diols (**126**) (Scheme 58) proceeded, in each case, with a high degree of diastereoselectivity (85T3519). Similar reactions have been reported with 3-vinylisoxazolines (85T5569; 90JOC3045). Esterases have been used to resolve isoxazolines. Modest discrimination between the enantiomers of the ester (**129**) was accomplished using pig liver esterase (90LA1013). The alcohol (**130**) was prepared in >90% enantiomeric excess through lipase-PS-catalyzed hydrolysis of butyl esters (92JOC2825).

VII. Uses of Isoxazolines

Isoxazolines have attracted interest in their own right. (*R,S*)-4,5-Dihydromuscimol (**132**) is a potent GABA agonist (79M11) and has been obtained through cycloaddition of bromonitrile oxide (**9**) with *N*-BOC-allylamine (**131**) (Scheme 59) (86TL4651; 90T1975). The individual enantiomers of the isoxazoline (**132**) were synthesized via reaction of bromonitrile oxide (**9**) with the dioxolane (*R*)-(**48b**) and separation of the diastereomeric products (90T1975). The structurally similar isoxazoline (**133**) was

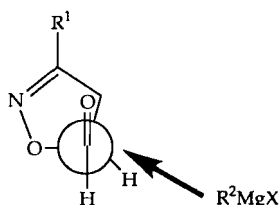
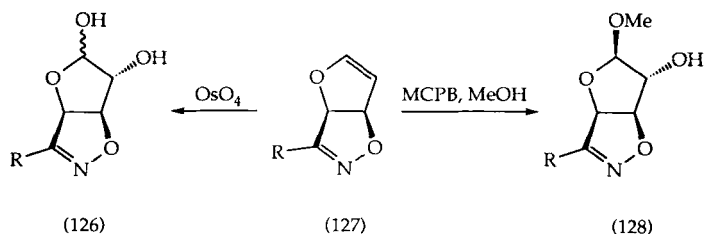
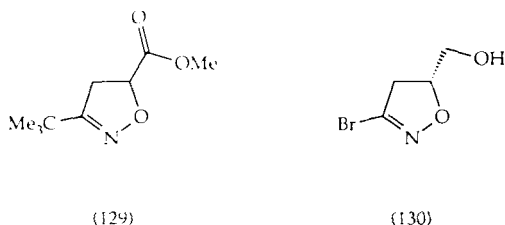


FIG. 6. Felkin-Ahn model for Grignard addition to 5-formyl-2-isoxazolines.



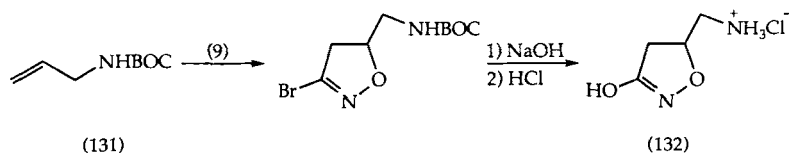
SCHEME 58

shown to be void of GABAergic activity (85JMC1109). The isoxazolines (134) display antifungal activity (91CCC1315, 91MI3). Others were investigated as antibiotics (90MI2), chemotherapeutic agents (91JOC1812), and peptide surrogates (92TL6811) and as analogues of prostaglandins (87MI1), steroids (90ZOR1274), and cocaine (91MI4), whereas the isoxazoline (135) is of interest in boron neutron capture therapy (92CC939).

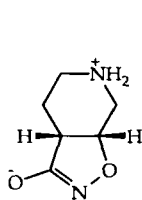


Much of the interest in isoxazolines stems from their use in the synthesis of other compounds. Work in this area has been reviewed (84ACR410; 84MI1; 90H719). Compound types previously obtained from isoxazolines (Scheme 60) continue to be accessed in this manner. Accordingly, syntheses of γ -amino alcohols (85CL1047, 85SC663; 89SC2237), β -hydroxy ketones [84JOC3474; 85TL4047; 86MI2; 87TL3189; 88ACS(B)303, 88BCJ2133, 88BCJ3973, 88KGS972, 88TL1307; 89BCJ171; 90JHC557; 91IZV969, 91TL683], α,β -unsaturated ketones (85SC663; 88TL2051) and β -hydroxy nitriles (90JOC3045), acids (84JOC3474), and esters (84JOC3474) have been reported.

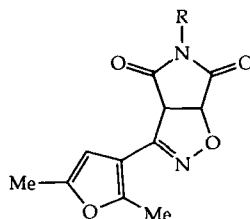
Steinmeyer and Neef (92TL4879) have used nitrile oxide cycloaddition, followed by ring-opening of the cycloadduct (138), to give the β -hydroxy ketone (139), and subsequent retroaldol cleavage to the ketone



SCHEME 59

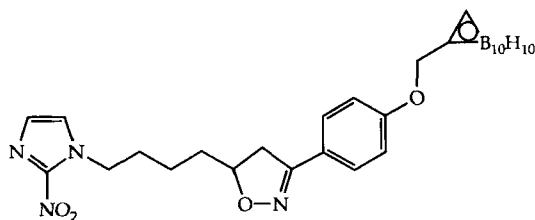


(133)



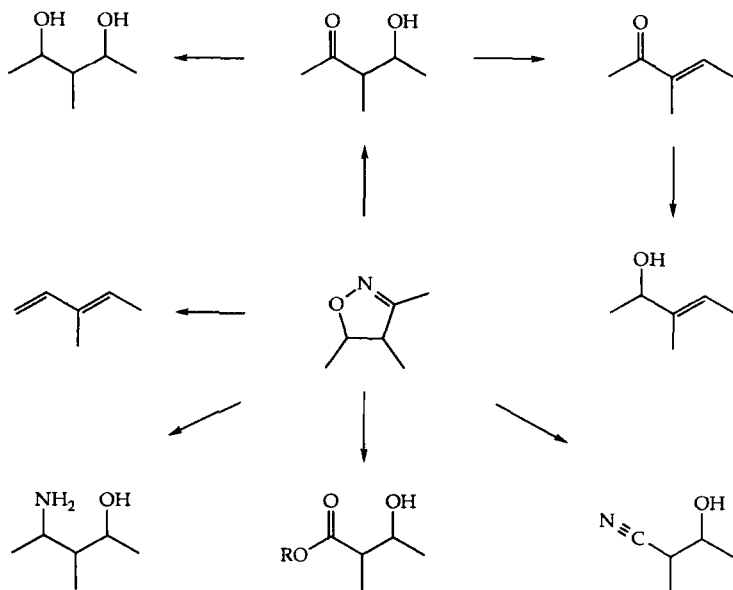
(134)

a) R = *p*-ClPh
or b) R = *o,o'*-Me₂Ph

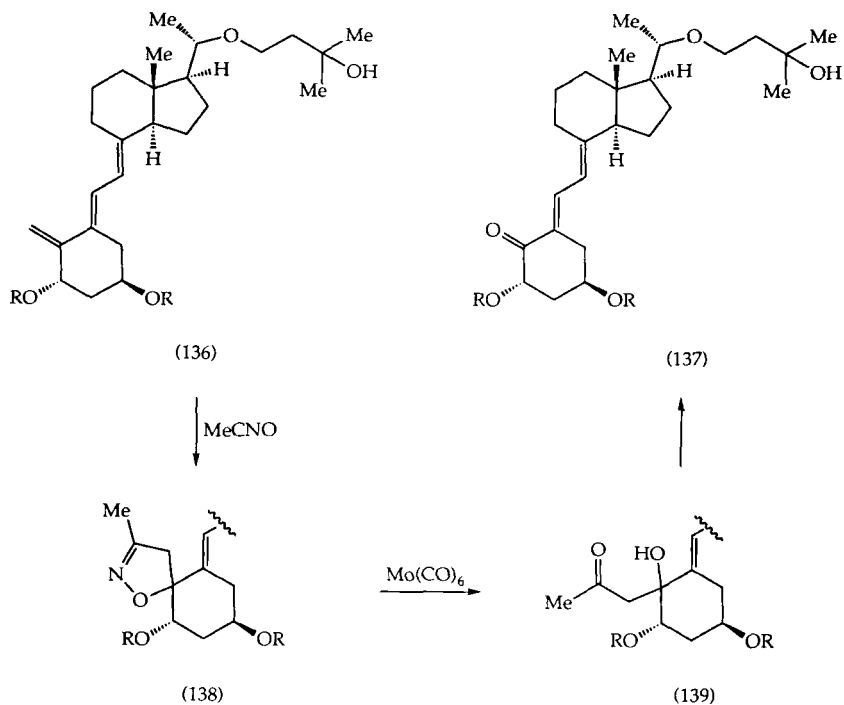


(135)

(137), to accomplish selective oxidation of the exocyclic methylene in the triene (136) (Scheme 61). The selectivity of this process is determined by the relative reactivity of alkenes toward cycloaddition with nitrile oxides.



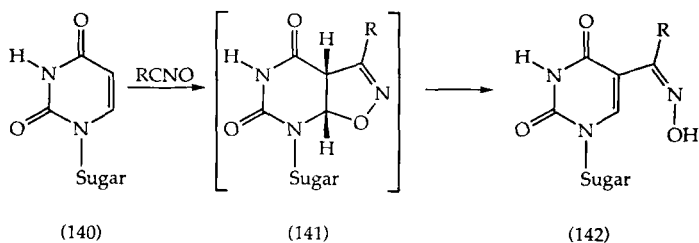
SCHEME 60



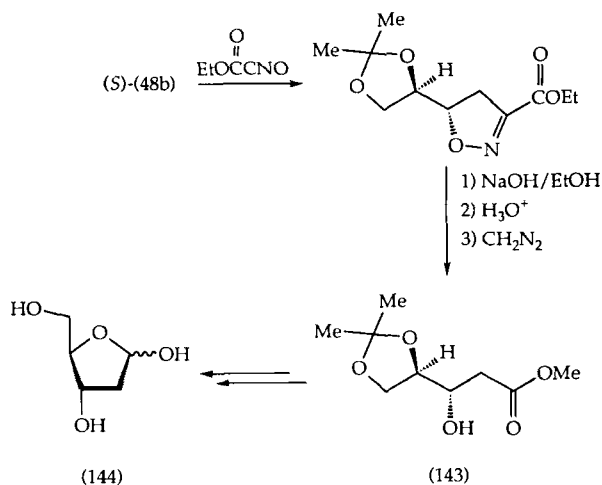
SCHEME 61

Cycloaddition of the nucleosides (**140**) followed by spontaneous ring-opening of the cycloadducts (**141**) gave the α,β -unsaturated oximes (**142**) (Scheme 62) (92JOC1088).

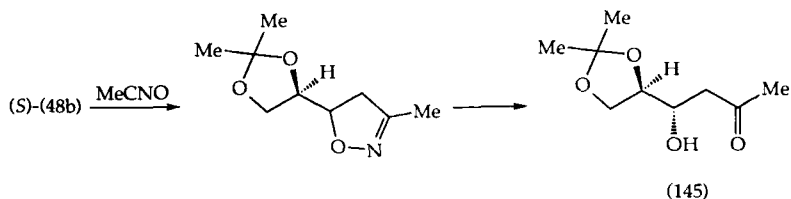
Much of the more recent work using isoxazolines involves stereocontrolled synthesis. Kozikowski and Ghosh (84JOC2762) used nitrile oxide cycloaddition to prepare the β -hydroxyester (**143**) and the β -hydroxyketone (**145**) from the dioxolane (*S*)-(48b) (Schemes 63 and 64). The ester (**143**) and ketone (**145**) are masked triols, suitable for use in the synthesis of sugars, as shown through the elaboration of the ester (**143**)



SCHEME 62

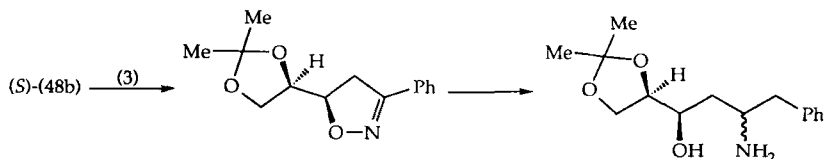


SCHEME 63

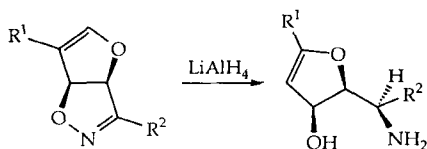


SCHEME 64

to 2-deoxy-D-ribose (**144**) (84JOC2762). Jäger and Schohe (84T2199) used the dioxolane *(S)*-(**48b**) in the stereocontrolled synthesis of γ -amino alcohols via isoxazolines (Scheme 65). The amino alcohols were then converted to amino sugars. Analogous elaboration of furoisoxazolines, coupled with stereoselective oxidation of the dihydrofuran ring, was used in the stereoselective synthesis of aminodeoxy furanosides (Scheme 66) (85T3519). Related syntheses involved a thiazole-substituted isoxazoline (88T3215) and stereocontrolled hydroxylation of the intermediate isoxazoline, before elaboration to the γ -amino alcohol (90S556). Stereoselective cycloaddition to the silyl ether (**146**) and alkylation of the cycloadduct



SCHEME 65

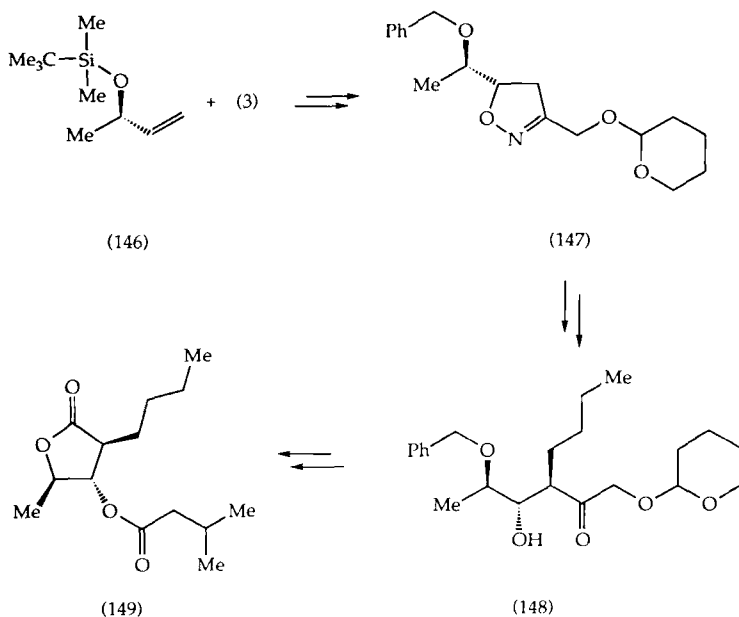


SCHEME 66

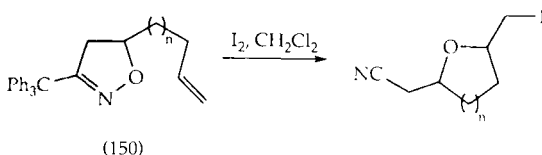
(147) followed by reduction gave the masked α,β',γ' -trihydroxyketone (148), which was used in the stereocontrolled synthesis of (\pm)-Blastmycinone (149) (Scheme 67) (84JOC2762).

Other stereocontrolled syntheses of γ -amino alcohols [91JCS(P1)2627, 91TL4171; 93TL2831], β -hydroxy ketones [85JOC778; 86S312; 87CL2229, 87JA3036; 88CC1339, 88TL6167; 89JOC2209; 90SC3575; 91CC132, 91JCS(P1)2627; 92MI2; 93JOC2173, 93TL2831], 1,3-diols (88TL6167; 91CC132; 93TL2831), and β -hydroxy nitriles (86TL3099), acids (91ACS736), and esters (91ACS736), via isoxazoles, have also been reported.

Elaboration of isoxazoles has been used in the synthesis of other heterocycles. Electrophilic cyclization reactions of 5-alkenyl-substituted isoxazoles (150) have been used in the synthesis of cyclic ethers (Scheme 68) (87JA7577; 90JOC283). Hydrogenolysis and decarboxylation of the



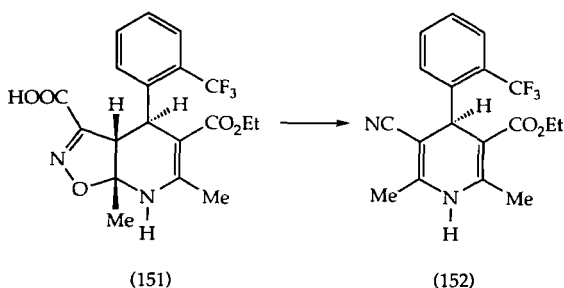
SCHEME 67



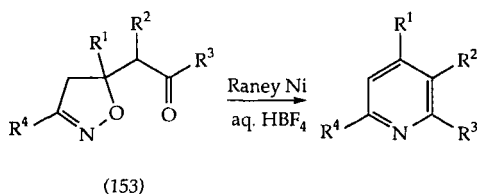
SCHEME 68

isoxazoline (**151**) gave the dihydropyridine derivative (**152**) (Scheme 69) (83JOC366; 89JOC5585). Reduction of 3-(β -ketoalkyl)-substituted isoxazolines (**153**) has been used in the synthesis of pyridines (Scheme 70) (91BCJ375). Thermolysis of the isoxazolines (**155**), prepared by cycloaddition of nitrile oxides with methylenecyclopropane (**154**), affords 5,6-dihydro-4-pyridone derivatives (**156**), presumably through initial homolysis of the nitrogen—oxygen bond of the isoxazolines (**155**) (Scheme 71) (85CC1518; 86CC813; 88JOC2426; 93MI1). The corresponding spirocyclobutylisoxazolines (**157**) afford azepin-4-ones (**158**) and *N*-alkenylpyrrolidin-2-ones (**159**) (Scheme 72) (86TL5271; 92T5283; 93MI1). Photolytic cleavage of the nitrogen—oxygen bond in the isoxazolines (**160**) resulted in rearrangement to the azabicyclo[4.3.0]nonadienedicarboxylates (**161**) (Scheme 73) (90CCC512).

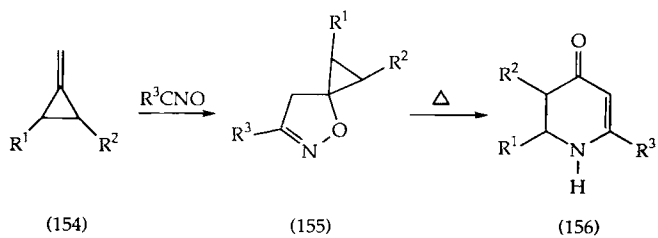
Although isoxazoles can be obtained by cycloaddition of nitrile oxides to alkynes (Scheme 74), they are also accessible via the corresponding isoxazolines. Dehydrogenation of isoxazolines has been carried out



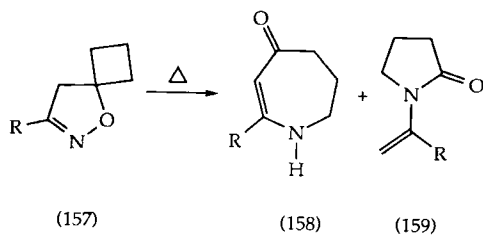
SCHEME 69



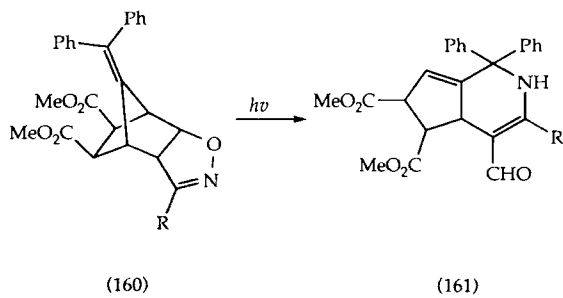
SCHEME 70



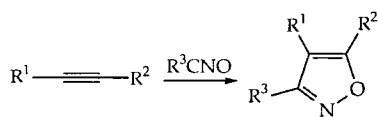
SCHEME 71



SCHEME 72

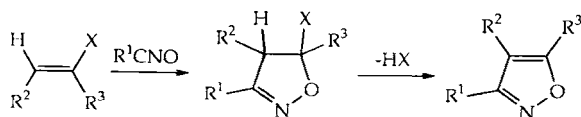


SCHEME 73

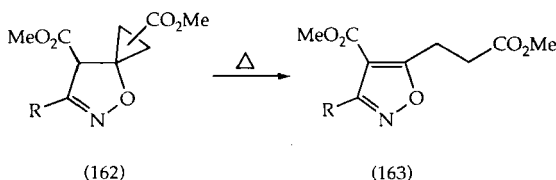


SCHEME 74

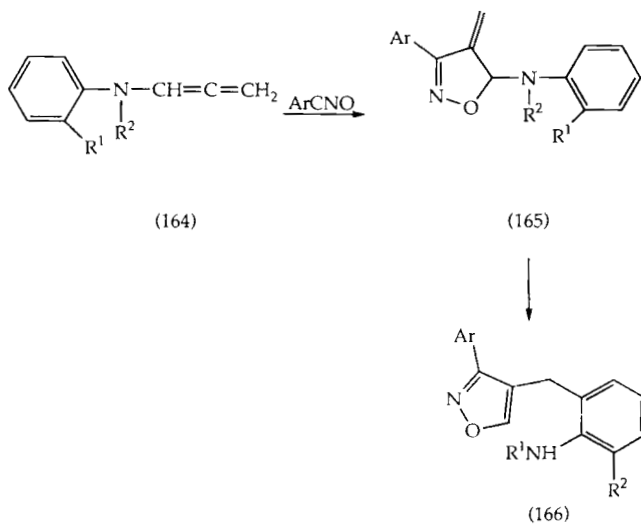
using chromic acid (1896JPC405), potassium permanganate (60JOC 1160; 79ZOR2436, 79ZOR2437), *N*-bromosuccinimide (65T817), Chloranil (74T3765; 76TL3983), 2,3-dichloro-5,6-dicyanobenzoquinone [79JCR(S)311], γ -active manganese dioxide (77S837; 78SC219), and air oxidation (74JCS(P)1757; 83H2181; 93TL4281). Alternatively, isoxazolines have been constructed with leaving groups suitable for subsequent elimination. Thus, chloro- (84BCJ1643), alkoxy- [84BCJ2216; 88ACS(B)303; 91JHC429; 92JHC251], methylthiyl- [84JCR(S)402], amino- [84JHC949, 84JHC1121; 85JHC797; 88ACS(B)303], trimethylsilyloxy- (85CL1047, 85CL1049), bromo- (87BCJ2463), imino- (90JHC2097), thiobenzamido- (90LA1013), acyloxy- (85JOC903; 90CJC1271, 90ZOR1274), vinylsulfonyl- [91JCS(P)2801], benzamido- (91JHC1945), *tert*-butyl- (92BCJ2484), and hydroxy-substituted [92H(34)1703] alkenes gave 5-substituted isoxazolines, which reacted by elimination to give the corresponding isoxazoles (Scheme 75). In unusual rearrangements, the spirocyclopropylisoxazoline (**162**) gave the isoxazole (**163**) on thermolysis (Scheme 76) (92T3323), and the cycloadducts (**165**) obtained from reaction of the allenes (**164**) with nitrile oxides underwent a Claisen-type rearrangement to give the corresponding isomers (**166**) (Scheme 77) [91JCS(P)1843]. The synthesis of isoxazoles via isoxazolines is particularly useful where the corresponding alkynes are inaccessible, as is the case, for example, with small ring systems, and positioning of the substituent of the alkene can be used to control the regioselectivity of the cycloaddition. Accordingly, the bromocyclohexenones (**167**) and (**169**) gave the corresponding regioisomeric cycloadducts (**168**) and (**170**) (Schemes 78 and 79) (94UP1).



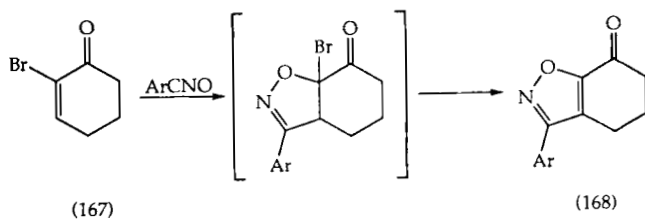
SCHEME 75



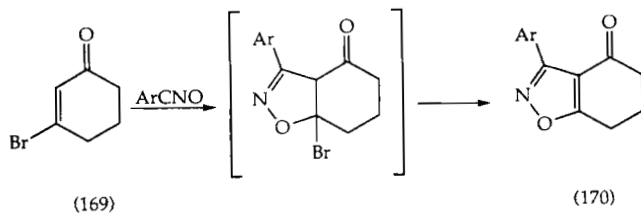
SCHEME 76



SCHEME 77



SCHEME 78

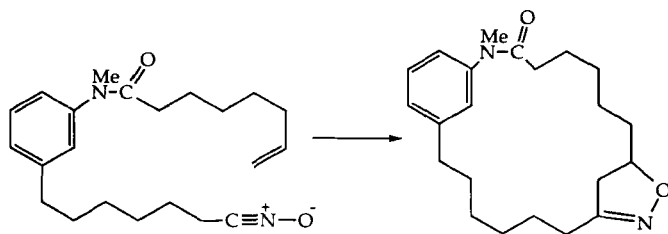


SCHEME 79

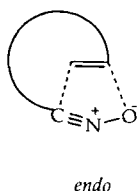
VIII. Intramolecular Nitrile Oxide Cycloadditions

Much of the recent work on nitrile oxide cycloaddition reactions with alkenes has involved intramolecular (INOC) processes. Whereas many aspects of the chemistry of INOC reactions are identical to those of the intermolecular analogues, others differ significantly as a result of the proximity of the reacting groups. Nitrile oxides are usually generated in similar fashion for use in intermolecular and intramolecular reactions; however, the predisposition of the alkene and the nitrile oxide within a molecule limits competing dimerization of the nitrile oxide in the latter case, with the result that less reactive alkenes undergo cycloaddition. Accordingly unactivated trisubstituted alkenes readily undergo INOC reactions (85CC847; 86CC757; 87CC189).

INOC reactions have been used in the synthesis of macrocycles (Scheme 80) (84TL947; 85BCJ2145, 85T3511). In these examples cycloaddition occurs in the *endo* mode (Fig. 7) and the nitrile oxide oxygen adds to the substituted carbon of the terminal alkene, as is the case with intermolecular reactions of monosubstituted alkenes. With most INOC reactions the regioselectivity is determined by geometric constraints, however, and reaction occurs in the *exo* mode (Fig. 8). Accordingly, ω -hexenyl [84ACR410, 84JOC2301; 85JA5310, 85TL2031; 87CC189, 87JA5280, 87JOC4674, 87T2369, 87TL4097; 88JOC50, 88JOC5590, 88TL715, 88TL4169; 89JA8954, 89JOC5277, 89T1517, 89TL5013; 90JOC5505, 90TL743; 91CB1181, 91JOC896, 91JOC5281, 91T3869, 91TL4259, 91TL5363; 93TL3017], heptenyl [84ACR410, 84JA1845, 84T2345; 85CC847, 85JA5310; 85JOC1564, 85TL43; 86CC757, 86TL1407; 87CC189, 87CC529, 87JOC3541, 87JOC4674, 87TL4097; 88JOC50, 88S342, 88TL715, 88TL4169; 89CC1093, 89JOC5277, 89TL5013; 90H597, 90JCS(P1)2481, 90JOC5505, 90TL743; 91CB1181, 91H1327, 91JOC896, 91MI1, 91T3869, 91T6635, 91T7537, 91TL3605, 91TL4259; 92H(33)73, 92H(33)161, 92TL4589], octenyl (84ACR410; 87CC189, 87TL4097; 88JOC50; 91CB1181, 91JOC896; 92TL1059), and decenyl (88CC198) nitrile

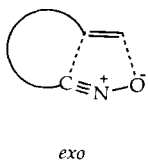


SCHEME 80

FIG. 7. The INOC reaction occurring in the *endo* mode.

oxides give solely the products of *exo* cycloaddition, irrespective of the degree of substitution of the alkene or of heteroatoms or the degree of hybridization in the alkyl chain. The transition states of INOC reactions of ω -hexenyl and heptenyl nitrile oxides have been modeled using a variety of methods (92JOC4862). Although there has been no systematic study of the geometrical constraints that result in *exo* cycloaddition and the minimum chain length required for the *endo* process, the ω -decenyl nitrile oxide (**171**) reacted solely in the *exo* mode (Scheme 81) (88CC198), whereas the ω -dodecenyl nitrile oxide (**172**) reacted only by *endo* cycloaddition (Scheme 82) (85BCJ2145). Formation of the fused cyclooctane (**173**) instead of the cyclohexane (**174**) is consistent with the effect of bond polarization to increase reactivity (Scheme 83) (84JA1845).

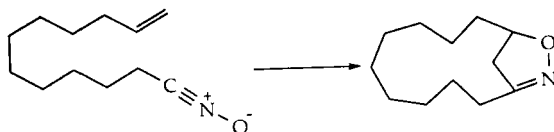
As is the case with their intermolecular counterparts, the stereochemistry of the alkene is retained in INOC reactions [84ACR410, 84T2345; 85JA5310; 87JOC4674, 87T2369; 90JCS(P1)533; 91TL3605]; this is illustrated in the reactions shown in Scheme 4 (85JA5310). The cyclic nitrile oxide (**175**) gave the tricyclic product (**176**) with complete control of stereochemistry at both new stereogenic centers (Scheme 84) (90H597). The latter reaction also involves face selectivity in the approach of the nitrile oxide to the alkene, which occurs commonly in the case of INOC reactions where the reactant is constrained by a preexisting ring (84ACR410, 84JA1845, 84JOC2301; 85TL43, 85TL2031; 86TL1407; 87JA5280, 87JOC3541; 89JOC5277, 89T1517; 91M11, 91TL3605; 93TL3017). Accordingly, the nitrile oxides (**177**), (**179**), and (**181**) gave only the isoxazolines (**178**) (85TL43), (**180**) (86TL1407), and (**182**) (91TL3605), respectively (Schemes 85–87).

FIG. 8. The INOC reaction occurring in the *exo* mode.



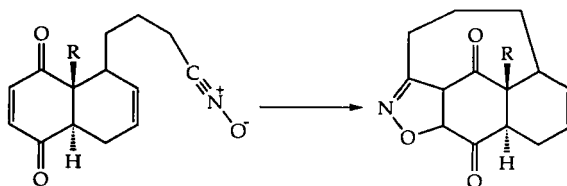
(171)

SCHEME 81

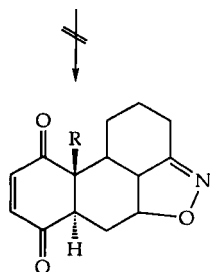


(172)

SCHEME 82

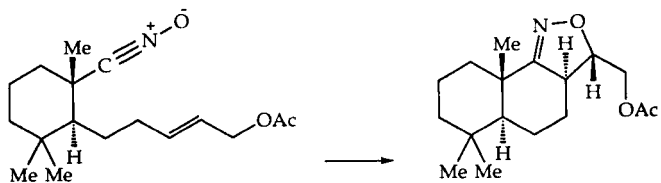


(173)



(174)

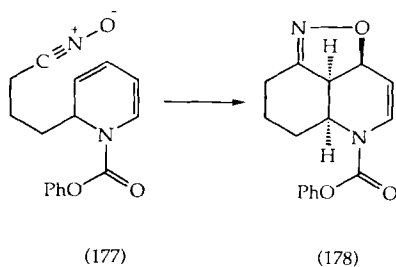
SCHEME 83



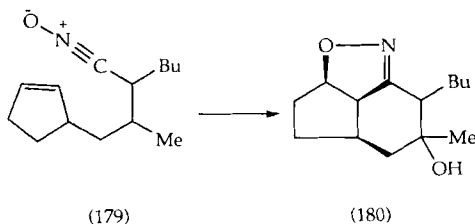
(175)

(176)

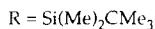
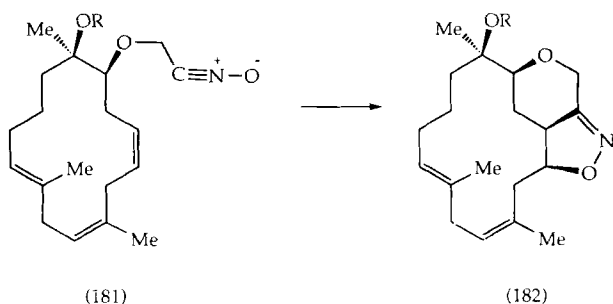
SCHEME 84



SCHEME 85

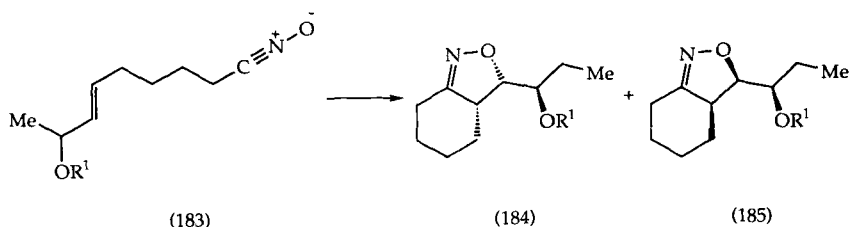


SCHEME 86

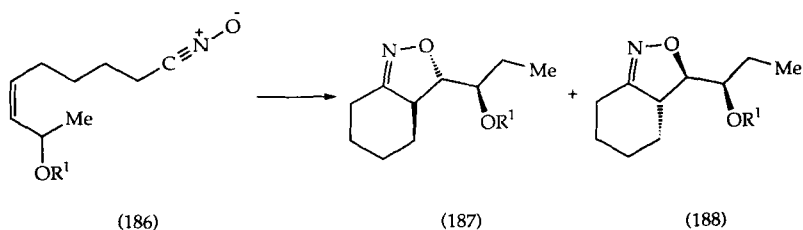


SCHEME 87

Annunziata *et al.* (87CC529, 87JOC4674, 87T2369) have examined the stereochemical outcome of INOC reactions where the alkene possesses a chiral allylic substituent remote from the nitrile oxide group. For example, the (*E*)-alkene (**183**) gave an 86:14 mixture of the diastereomers (**184**) and (**185**) (Scheme 88), whereas the corresponding (*Z*)-alkene (**186**) afforded the cycloadducts (**187**) and (**188**) in the same ratio (Scheme 89) (87CC529, 87JOC4674). Theoretical calculations have been used to ratio-

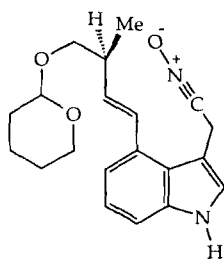


SCHEME 88



SCHEME 89

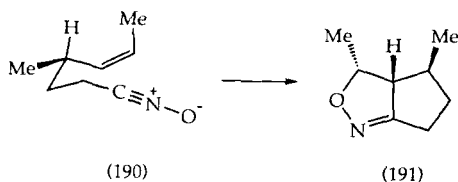
nalize the stereoselectivity observed in reactions of this type (87JOC4674; 92TL4409). The degree of stereoselectivity in these systems is quite variable, however, being negligible in the reaction of the nitrile oxide (189) (84T2345).



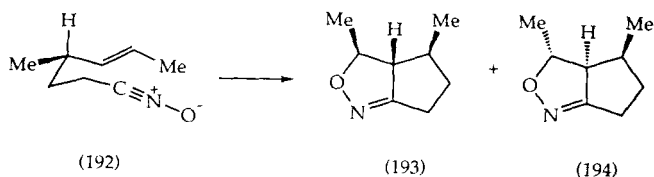
(189)

An allylic chiral center between the nitrile oxide and alkene groups can also affect the stereochemistry of INOC reactions. For example, the production of only the cycloadduct (191) in the reaction of the (*Z*)-nitroalkene (190) (Scheme 90), compared to the formation of a 3 : 1 mixture of the isoxazolines (193) and (194) from the (*E*)-isomer (192) (Scheme 91) (84ACR410) is a dramatic example of the influence of allylic 1,3-strain (89CRV1841) on these processes.

A chiral center adjacent to the nitrile oxide is also known to affect INOC reactions, as illustrated in the formation of the isoxazoline (195a),



SCHEME 90

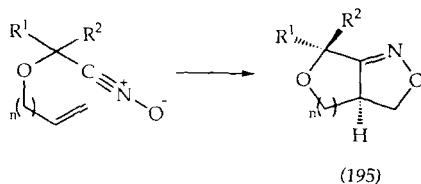


SCHEME 91

as a single diastereomer (Scheme 92) (88TL4169). By comparison, the homologue (**195b**) was obtained in 70% diastereomeric excess (Scheme 92) (89JOC5277). Theoretical calculations were used to rationalize the opposite stereochemical outcome of these reactions and similar observations in related systems (90JOC5505, 90TL743; 91CB1181; 92TL4405). Remote substituents can affect the diastereoselectivity of these processes, as illustrated in the production of only the isoxazolines (**197**) and (**198**), as an 11 : 1 mixture, in the reaction of the diene (**196**) (Scheme 93) (91TL4259).

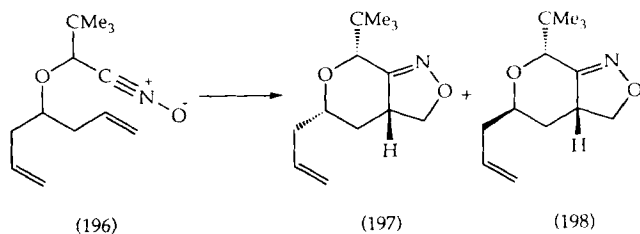
INOC reactions of substrates with multiple chiral centers have also been reported [88JOC5590; 92H(33)161]. The heptose derivative (**199**) gave the cycloadducts (**200**) and (**201**) (Scheme 94) as a 64 : 36 mixture, whereas the diastereomeric nitrile oxide (**202**) gave only the isoxazoline (**203**) (Scheme 95) (91T7537). The phthalimide (**204**) gave only a single product (Scheme 96) (91TL5363), whereas the pyranose derivative (**205**) gave the isoxazoline (**206**) (Scheme 97) in 89% diastereomeric excess (92TL1059).

Hassner *et al.* have investigated the stereochemical consequences of cyclization of vinyl-substituted azetidines and azetidinones. The vinylazet-

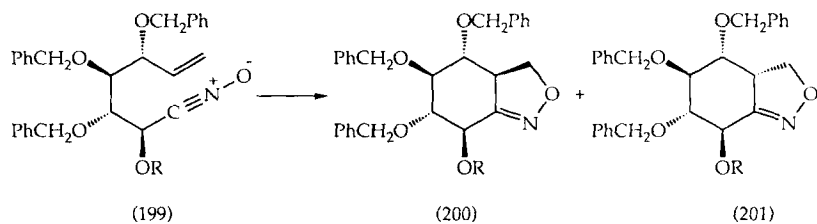


- a) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $n = 1$
 b) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, $n = 2$

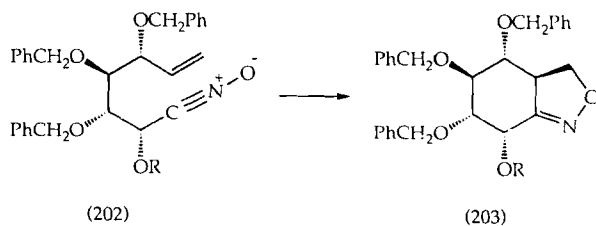
SCHEME 92



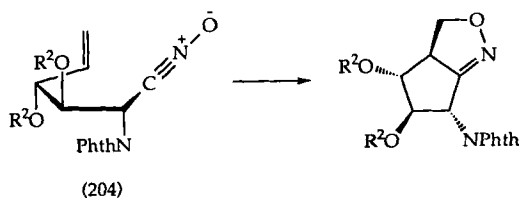
SCHEME 93



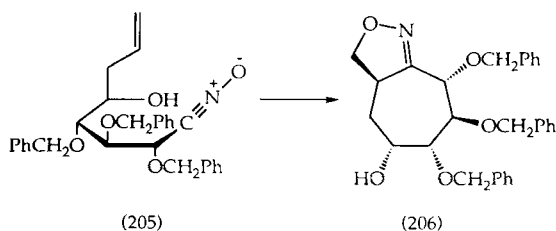
SCHEME 94



SCHEME 95

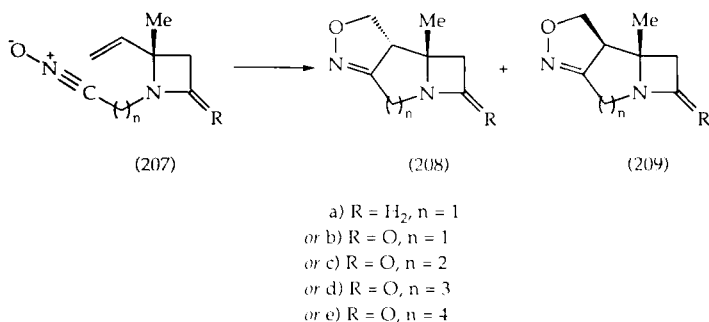


SCHEME 96

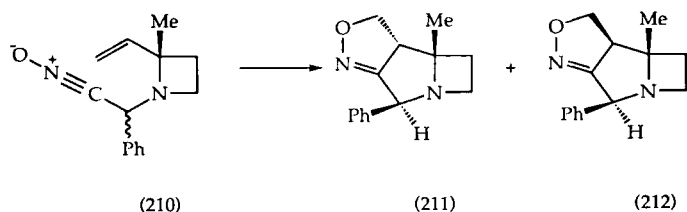


SCHEME 97

idine (**207a**) gave a 2:1 mixture of the fused cyclopentanes (**208a**) and (**209a**) (Scheme 98) (87TL4097). The azetidinones (**207b**) and (**207e**) failed to cyclize, the cyclohexane (**209c**) was produced as a single diastereomer, and the fused cycloheptanes (**208d**) and (**209d**) were obtained as a 2:3 mixture (Scheme 98) (88JOC5063). The stereospecific formation of the cyclohexane (**209c**) is consistent with reaction via a chair transition state, whereas the poor stereoselectivity in the reactions to give the cycloheptanes (**208d**) and (**209d**) reflects the greater flexibility in the corresponding transition states. In the case of the azetidine (**210**), only the diastereomer leading to the isoxazolines (**211**) and (**212**) underwent cycloaddition (Scheme 99) (87TL4097). Chair-like transition states have been used to rationalize the stereochemical outcome of a variety of other INOC reac-



SCHEME 98



SCHEME 99

tions that afford fused cyclohexanes [90H597, 90JCS(P1)2481, 90JOC4497; 91T6635].

A major impetus for continued interest in INOC reactions has been their utility in synthesis. Accordingly, γ -hydroxy amines (84ACR410, 84T2345; 90JOC5505; 93TL3017), β -hydroxy imines (86CC757, 86TL4865; 89T1517), β -hydroxy ketones [84JOC2301, 84TL947; 85BCJ2145, 85CC847, 85JOC1564, 85T3511, 85TL43, 85TL2031; 86CC757, 86TL1407, 86TL4865; 87CC189, 87JA5280, 87JOC3541, 87T2369; 88JOC5590; 89BCJ602, 89CC1093, 89T1517; 90H597, 90JCS(P1)2481, 90JOC4497; 91H1327, 91JOC5281, 91MI1, 91T6635, 91TL3605, 91TL5363; 92H(33)161, 92TL1059, 92TL4589], and α,β -unsaturated ketones (86TL1407; 87JA5280, 87JOC3541; 88CC198; 89JA8954) have been reported in this manner.

In this chapter we have attempted to summarize recent trends in nitrile oxide cycloaddition reactions of alkenes. We hope that this overview will stimulate and encourage continued work in the field.

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The nomenclature of compounds listed in this index follows the usage of the authors of the chapters and not necessarily the strict IUPAC or *Chemical Abstracts* style. However, when a chemical name as used by the authors is widely divergent from accepted usage, the more appropriate name has been marked with an asterisk to alert the user that the index entry may not appear in the text on the page indicated. To keep entries brief, "obvious" details, such as indicated hydrogen in its usual or only possible place, have been omitted.

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